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Review

Soluble Fas ligand, soluble Fas receptor, and decoy receptor 3 as disease biomarkers for clinical applications: A review

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Abstract: Soluble Fas ligand (sFasL, sCD95L) and its specific soluble binders, soluble Fas receptor (sFas, sCD95) and decoy receptor 3 (DcR3), have been investigated as possible clinical biomarkers in many serious diseases. The present review aimed to provide an overview of the current state of this medically promising research by extensively examining the relevant literature. The summarized results of the survey are presented after classification into six categories according to the type of targeted disease. To date, the studies have been mainly devoted to the diagnosis of disease severity states and prognosis of treatments about various types of cancers and autoimmune diseases represented by autoimmune lymphoproliferative syndrome and systemic lupus erythematosus, because these important life-threatening or intractable diseases were suggested to be most relevant to the impairment of apoptotic cell death-inducing systems, including the Fas receptor-mediated signaling system, and the mechanisms responsible for their onset. However, various more general inflammation-related diseases, including, but not limited to, other autoimmune and allergic diseases (e.g., rheumatoid arthritis and atopic asthma), infectious diseases (e.g., sepsis and chronic hepatitis), cardiovascular system-specific disorders (e.g., acute coronary syndromes and heart failure) as well as other diseases specific to the renal, hepatic, and respiratory systems, etc., have also been targeted as important fields of research. The data obtained so far demonstrated that sFas, sFasL, and DcR3 possess significant potential in the assessment of various disease states, which can contribute to the development of therapeutic interventions. Although further studies in various relevant fields are essential, it is expected that clinical translation of sFas, sFasL, and DcR3 into practical biomarkers will contribute to effective treatments of a wide variety of diseases.

Keywords: Fas ligand (CD95L); Fas receptor (CD95); decoy receptor 3; soluble disease biomarker

Abbreviations used in main text: ACLF: Acute-on-chronic liver failure; ACS: Acute coronary syndrome; AD: Alzheimer's disease; ADA: Adenosine deaminase; ADPKD: Autosomal dominant polycystic kidney disease; AGVHD: Acute graft-versus-host disease; AHI: Apnea-hypopnea index; AHSCT: Allogeneic hematopoietic stem cell transplantation; AKI: Acute kidney injury; ALT: Alanine aminotransferase; ALPS: Autoimmune lymphoproliferative syndrome; AMD: Age-related macular degeneration; AMI: Acute myocardial infarction; APACHE: Acute physiology and chronic health evaluation; AR: Acute rejection; ARDS: Acute respiratory distress syndrome; AS: Ascites; BLC: Bladder cancer; BMI: Body-mass-index; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CB: Cord blood; CCC: Coronary collateral circulation; CHD: Coronary heart disease; CIR: Cirrhosis; CKD: Chronic kidney disease; CLC-PH: Compensated liver cirrhosis accompanied with portal hypertension; COPD: Chronic obstructive pulmonary disease; COVID-19: SARS-CoV-2 virus; CR: Clinical remission; CRP: C-reactive protein; CSF: Cerebrospinal fluid; CVD: Cardiovascular disease; DcR3: Decoy receptor 3; DFL: Diabetic foot lesions; DISC: Death-inducing signaling complex; DM: Diabetes mellitus; ECD: Extracellular domain; eGFR: Estimated glomerular filtration rate; EPO: Erythropoietin; ESA: Erythropoietin-stimulating agent; ESRD: End-Stage renal disease; EVD: Ebora virus disease; FADD: Fas-associating protein with death domain; FasL: Fas ligand; FL: Flare; GD: Graves' disease; GH: Graves' hyperthyroidism; GIST: Gastrointestinal stromal carcinoma; GO: Graves' ophthalmopathy; Hb: Hemoglobin; HBV: Hepatitis-B virus; HCC: Hepatocellular cancer; HCV: Hepatitis-C virus; HD: Hemodialysis; HDC: Hydrocephalus; HF: Heart failure; HFRS: Hemorrhagic fever with renal syndrome; HIE: Hypoxic-ischemic encephalopathy; HIV: Human immune-deficiency virus; HNC: Head and neck cancer; HRT: Hormone replacement therapy; HYP: Hypertension; IFN: Interferon; IL: Interleukin; IPH: Intraparenchymal hemorrhage; IS: Ischemic stroke; IUGR: Intrauterine growth restriction; KD: Kawasaki disease; LF: Liver fibrosis; LN: Lupus nephritis; MCI: Mild cognitive impairment; MELD: Model for end-stage liver disease; METS: Metabolic syndrome; MS: Multiple sclerosis; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; NH: Non-hemorrhagic; NNAG: Nonagenarians; Non-RS: Non-resolving subphenotype; O_2T: Oxygen-gas treatment; PE: Pleural effusion; PH: Post-hemorrhagic; PKTR: Pediatric kidney transplant recipients; PL: Plasma; PMS: Postmenopausal syndrome; PPCM: Peripartum cardiography; PRC: Prostate cancer; PRF: Preserved renal function; PTE: Pulmonary thromboembolism; PVL: Periventricular leukomalacia; RA: Rheumatoid arthritis; RCC: Renal cell cancer; RRMS: Relapsing-remitting MS; SAL: Saliva; SCD: Sickle cell disease; SF: Synovial fluid; sFas: Soluble Fas receptor; sFasL: Soluble Fas ligand; SIRS: Systemic inflammatory response syndrome; SJS: Stevens-Johnson syndrome; SLE: Systemic lupus erythematosus; SOFA: Sequential organ failure assessment; SR: Serum; STC: Stomach cancer; TNF: Tumor necrosis factor; SS: Sjögren's syndrome; SUH: Subarachnoid hemorrhage; T1DM: Type-1 DM; T2DM: Type-2 DM; T/AB: Tau protein/amyloid β 1-42 ratio; TB: Tuberculosis; TEN: Toxic epidermal necrolysis; TRAb: Thyroid stimulating hormone receptor antibodies; TEN: Toxic epidermal necrolysis; VO_2-max: Peak oxygen consumption; VED: Vascular endothelial dysfunction; WS: Werner syndrome; %fat: Percent body fat

Abbreviations used in Tables' columns for assay methods and statistical indices: AUC: The area under the curve; b: Regression coefficient; Corr.: Correlation analysis; C statistic: Concordance statistic; CV: Cutoff value; DDA: Double determinant immunoassay; ELISA: Enzyme-linked immunosorbent assay; HR: Hazard ratio; Iqr: Interquartile range; LC-ESI MS: Liquid

chromatography-electrospray ionization mass-spectrometry method; Md: Median; Mn: Mean; MPAA: Multiplex array assay; nd: Not described; ns: Not significant; OR: Odds ratio; p: Probability value; PEA: Primer extension assay; r: Pearson's correlation coefficient; r_s: Spearman's correlation coefficient; r^2: Determination coefficient: Rg: (whole) Range; ROC curve: Receiver operating characteristic curve; RR: Risk ratio; SD: Standard deviation; SEM: Standard error of the mean; WB: Western-blotting method; 95% CI: 95% Confidential interval

1. Introduction

The occurrence of numerous life-threatening or quality of life devastating diseases may originate from various impairments in controlling physiologically essential cell death and inflammation [1]. The Fas receptor (Fas, CD95)-mediated signaling system triggered by Fas ligands (FasL, CD95L) plays a pivotal role in apoptotic cell death through extrinsic pathways in the human body. Dysfunctions of the cell death-inducing system caused by mutations in the Fas and FasL genes are directly involved in the onset of malignant tumors such as multiple myeloma and non-Hodgkin's lymphoma as well as some serious autoimmune diseases such as autoimmune lymphoproliferative syndrome (ALPS) and systemic lupus erythematosus (SLE) [2].

Both Fas ligand and Fas receptors are cell-surface localized proteins that contain a single transmembrane domain per monomer unit. On the other hand, decoy receptor 3 (DcR3) is produced as a soluble protein, which does not contain any membrane-binding region in its primary sequence [3]. From a structural point of view, soluble Fas ligand (sFasL) and soluble Fas receptor (sFas) correspond to the extracellular domain (ECD) regions of FasL and Fas receptor, respectively. In the induction of apoptotic cell death triggered by FasL, the binding of FasL-ECD to Fas-ECD induces the trimerization of cell-membrane-bound Fas receptor in the target cells, and this process further elicits the formation of death-inducing signaling complex (DISC) through the binding of Fas-associating protein with death domain (FADD) and procaspase 8/10. DcR3 binds specifically to FasL-ECD with an affinity comparable to that of the Fas receptor (Kd = 0.8 nM) [2]. sFas, sFasL, and DcR3 ordinarily function as competitive inhibitors in the implementation of Fas receptor-mediated apoptosis, unless otherwise sensitized with either endogenous intracellular factors or exogenous extracellular agents [4]. According to widely accepted mechanisms, sFas and sFasL are produced by an alternative gene-splicing accompanying deletion of the transmembrane domain [5] and by shedding from the corresponding membrane-bound form with extracellular metalloproteinases such as MMP3, MMP7, MMP9, and ADAM10 [6], respectively. In humans, the apoptotic activity of FasL is greatly reduced by cleavage of its stalk region with MMP7 [7], while the resulting sFasL may trigger non-apoptotic biological functions, including metastasis in triple-negative breast cancer [8].

It is possible that the expression levels of inhibitory soluble protein factors involved in Fas-mediated apoptosis in human body fluids are significantly related to the pathogenic process; therefore, they could be biomarkers reflecting the status of diseases. The expression levels of sFas, sFasL, and DcR3 are significantly upregulated in many body-fluid samples such as the blood serum (SR)/plasma (PL) and synovial fluid obtained from patients with cancer and rheumatoid arthritis, respectively [6,9–11]. It would be reasonable to expect that the concentration of the above-mentioned soluble proteins in body fluids are also attractive candidates as effective biomarkers for obtaining useful information on the clinical status of more general diseases whose onset may be related to the abundance of cell death-affecting proteins. Multiple pieces of fundamental evidence have been

obtained for the interrelationship between Fas ligand-induced apoptotic cell death and inflammation, mediated by caspases and interleukin (IL)-1β [1,12,13]. Consequently, the usability of sFas, sFasL, and DcR3 in diagnosing disease severity, evaluating treatment efficacy, and predicting the prognosis of future outcomes have been investigated for a wide range of inflammation-related diseases by statistically analyzing various clinical indices concerning these soluble biomarkers. However, despite their potential usefulness and researchers' endeavors, translational processes into practical applications as decision-making parameters for therapeutic intervention at the bedside are still underway. In this review, an extensive survey of the possible uses of sFas, sFasL, and DcR3 was conducted to summarize the current knowledge on the applicable range of these soluble proteins as disease biomarkers for treatment in clinical medicine.

2. Literature review

The extensive literature review collected references using a combination of the following key words: "soluble fas," "ligand," "receptor," "DcR3," "diseases," "cancer," "autoimmune," and "biomarkers," using PubMed, Web of Science, and Google Scholar as the main search engines. The selection criteria was based on the close relation to the scientific aim and scope of this survey as well as the free accessibility to the article contents and relevant statistical indices. Tables 1 to 6 summarizes target markers and diseases, primary findings, cohort characteristics, evaluation methods used, and obtained representative statistical indices. Abbreviations are used to make the individual rows self-explanatory in the tables. A "ca." precedes each of the observed values, which are not directly described as texts but estimated from the reference papers, as statistical indices. The results of the survey are presented in chronological order after classification into six sections: cancers, autoimmune and allergic diseases, infectious diseases, cardiovascular and hematologic systems-specific diseases, non-cardiovascular/hematologic systems-specific diseases, and other miscellaneous diseases. Where appropriate, the contents of the sections were further divided into subsections.

3. sFas, sFasL, and DcR3 as clinical biomarkers for diseases

3.1. Cancers [14–78]

Table 1 summarizes studies on the potential use of sFas, sFasL, and DcR3 as clinical biomarkers for various types of cancers and targeted organs. The varying directions and ranges in the body fluid levels of sFas, sFasL, and DcR3 depended considerably on the types of malignancies and clinical states of the diseases. However, in many cases, the levels of the above soluble markers in patients with cancer were significantly upregulated or downregulated compared with those in healthy controls, and progressively changed as the disease severity entered advanced stages. The main findings concerning individual primary organ-derived cancers are briefly summarized in the following sections.

Among various types of cancers, breast cancer has been one of the most frequently investigated types of malignant tumors to date. SR/saliva (SAL) sFas, sFasL, and DcR3 levels in patients with breast cancer are often significantly higher than those in patients with benign breast tumors or healthy controls [14,22,41,50,58,59,64,66,69,78]. In general, patients at more advanced metastatic stages tend to have significantly higher levels than those in the less-advanced stages. However, contradictory results concerning SR sFasL levels presented significantly lower SR sFasL levels in breast cancer

patients than those in healthy controls and decreasing SR sFasL levels associated with increasing tumor stage [40,41]. SR sFas levels may be helpful for early detection of malignant lesions, since patients have significantly higher levels of SR sFas than those of healthy controls [64]. The SAL sFas level showed a diagnostic power similar to that of the common cancer antigen CA125 for breast cancer [78]. SR sFas and sFasL levels in breast cancer patients may help clinicians predict response [37] or evaluate the efficacy of chemotherapy [58,59].

The next highest number of studies focused on cancers originating from the colon/rectum [23,25,38,49,60,62,63,65,72], ovaries [16,21,31,33,34,39,42,45], stomach [17,23,27,38,43,57,66], liver [23,38,47,48,51,55,61], and lungs [23,24,26,38,46,52]. Significantly higher SR DcR3 and sFas levels are found in patients with colorectal cancers than those in healthy individuals, however, the distinct differences between benign diseases and malignant colorectal cancers were not always observed [60,62,63]. SR sFas levels discriminated between metastatic and non-metastatic subgroups [63], and SR DcR3 levels were associated with multiple disease severity indices, including lymph node and distant metastasis [62]. The sFas/sFasL ratio may be an excellent dynamic chemosensitivity marker for following up the response to oxaliplatin-5-fluorouracil treatment [25]. Interestingly, SR sFas levels in patients with colorectal polyps, but not those in patients with malignant tumors, were significantly higher than those in healthy controls [65].

As for ovarian cancer, controversial results on the relationship between SR sFas or DcR3 levels and the presence of the tumor have been obtained. SR sFas or DcR3 levels in patients with malignant tumors can be significantly higher than those in patients with benign tumors or healthy controls, including surgically normal subjects [16,31,42]; however, no significant statistical difference was observed [21,39,45]. This discordance may be explained by the differences in the disease stages of the targeted patients and characteristics of the tumor. Apart from the general dependence of SR sFas and DcR3 levels on the tumor stages [16,31,42], basal and postoperative SR sFas as well as ascites (AS) DcR3 levels are significantly associated with the responsiveness of the tumors to chemotherapy with platinum-based anti-cancer drugs [33,34]. SR DcR3 levels may improve early tumor detection in combination with CA125 [31].

In stomach cancers (STC), SR sFas and DcR3 levels are significantly higher than those in precancerous or non-tumoral groups [43,66]. SR sFas levels may be a noninvasive tool for the early detection of STC [43]. In contrast, SR sFasL and DcR3 levels served as prognostic parameters, since significantly higher SR sFasL and SR DcR3 levels were observed after entering advanced tumor stages [17,23]. SR sFasL levels were significantly higher in female than those in male patients, while the difference in *Helicobacter pylori* infection status did not provide a statistically significant variation in SR sFasL levels in STC patients, irrespective of the gender [27]. In patients with metastatic gastrointestinal stromal carcinoma (GIST), hand-foot skin reactions were associated with elevated PL sFasL levels. The symptoms were significantly correlated with PL sFasL concentration after sunitinib treatment [57].

The SR sFas, sFasL, and DcR3 levels in hepatocellular cancer (HCC) patients with severe hepatic impairments such as top or decompensated degree of liver cirrhosis (CIR) commonly exhibit significantly higher values than those in patients with chronic liver disease without CIR [47,48,51,55,61]. The SR levels of the biomarkers were reliable diagnostic parameters for the prediction of the outcome of HCC patients, since they significantly increased as the disease severity, defined by either TNM or other staging systems, progressed. Further, SR DcR3 levels were useful for early HCC diagnosis, since

these levels were already elevated in the patients at the precancerous or early stages in comparison to those in patients with cholecystitis or healthy controls [47].

Both SR sFas and sFasL levels were significantly higher in patients with small-cell lung cancer than those in healthy controls; however, only the SR sFas level was an effective marker for tumorigenesis, metastasis, and prediction of chemotherapy responsiveness [26]. SR sFas levels in patients with various types of lung cancer, including squamous cell carcinoma, adenocarcinoma, and small cell carcinoma, were significantly higher than those in patients with benign lung diseases, including asthma and chronic obstructive lung disease, and healthy controls [46]. The SR sFas level was also identified as one of the five best markers for prediction of males, but not females, at risk of non-small-cell lung cancer [52]. Mean levels of bronchoalveolar lavage fluid sFas and sFasL in patients with unspecified types of lung cancer were higher than those in healthy controls, but no statistical significance was recorded [24].

The usability of sFas, sFasL, and DcR3 levels as clinical biomarkers on uterine, head and neck, pancreatic, and bladder cancers was also reviewed. SR sFas, but not always sFasL, levels in patients with uterine cancers, including cervical cancer and endometrial cancer, are commonly higher than those in healthy controls [16,28,32,70]. SR sFas levels in patients with cervical cancer are significantly elevated, even at the precancerous stage of mild dysplasia [32]. An SR sFas level of less than 1.5 ng/ml was identified as the threshold value for the absence of death in patients with both cervical and endometrial cancers, but a statistically significant difference in survival rate using this criterion was only observed for patients with cervical cancer [16]. Cervicovaginal lavages sFas and sFasL in patients with invasive cervical cancer also significantly increased compared to non-invasive cervical cancer with intraepithelial lesions alone and healthy controls [70]. SR sFas and SR sFasL levels in patients with head and neck cancer (HNC) showed the opposite trend. The former and latter were significantly higher and lower, respectively, than those in healthy controls [20,44,74,77]. SR sFas levels showed a gradual increase in patients with HNC with more advanced tumor stages and less differentiated tumors, but with no statistical significance [44]. Surgical removal of the tumors substantially decreased and increased SR sFas and SR sFasL levels in HNC patients, respectively. SR Fas [44] and SR sFasL [20] levels in patients who appear tumor-free with squamous cell-type HNC after surgery were comparable to those of healthy controls. SR sFasL levels in cisplatin-drug-administered HNC patients co-treated with pantoprazole to reduce nephrotoxicity were significantly lower than those in patients without the cotreatment [77]. SR DcR3 levels in patients with pancreatic cancer were significantly elevated compared with those in healthy controls. The DcR3 levels presented a significant positive correlation with the expression levels of DcR3 in tumor tissues, and elevated tissue levels were associated with more severe disease activity and shorter overall survival [71]. In patients with poorly differentiated pancreatic neuroendocrine tumors, SR/PL sFasL levels were significantly lower than those in healthy controls, and these levels showed a significant negative correlation with the expression levels of a cell growth fraction marker, Ki-67 antigen index [73]. SR sFasL levels in patients with bladder cancer (BLC) were significantly higher than those in healthy controls, and the higher levels were positively correlated with advanced histologic stage and clinical grade of the tumor [18]. Urine sFas level in patients with BLC was identified as a useful biomarker for the detection of the presence and aggressiveness of non-invasive superficial tumors [29] as well as for the diagnosis of BLC caused by bilharzial infection [53].

A limited number of investigations have been conducted on primary tumors originating from the prostate [41,56], kidney [36,76], gallbladder/biliary tract [38,75], thyroid [23,54], lymphocytes [15,66],

skin [19], esophagus [35], and testis [30]. SR sFas levels and SR sFasL levels in patients with prostate cancer (PRC) were reported to be significantly higher and lower, respectively, than those in healthy controls [41]. SR sFas levels in patients with PRC was a useful diagnostic marker that can distinguish PRC from benign prostate hyperplasia with high sensitivity and specificity [56]. SR DcR3 levels in patients with non-metastatic renal cell cancer (RCC) at advanced tumor stages and in those with metastatic tumor at any stage were significantly elevated compared to those in healthy controls, suggesting the feasibility of DcR3 level as a prognostic biomarker in RCC [36]. However, no significant difference in SR sFasL levels was observed between patients with metastatic RCC before and after treatment and the tyrosine kinase inhibitor axitinib [76]. A decrease in SR sFasL levels in patients with unresectable or metastatic biliary tract cancer was significantly associated with responsiveness to combined chemotherapies based on an immune checkpoint inhibitor, nivolumab, resulting in longer overall survival [75]. PL sFasL levels in patients with differentiated thyroid cancer were significantly associated with disease recurrence, and sFasL levels were also useful for the assessment of progression-free survival of patients [54]. Patients with aggressive non-Hodgkin's lymphoma, especially those with B symptoms such as high fever, night sweating, and loss of body weight, had significantly elevated SR sFas levels compared to those in healthy controls [15]. Elevated SR sFas levels in patients with melanoma are significantly associated with overall and progression-free survival [19]. SR sFasL levels in patients with esophageal cancer was a good discriminator from benign gastroesophageal reflux controls with the highest sensitivity and specificity among 53 cancer-related protein markers [35]. SR sFasL levels in patients with testicular germ cell tumors were not significantly different from those in healthy controls [30].

When targeting various cancers simultaneously, including bone and larynx cancers, in addition to the cancer types mentioned above, SR DcR3 levels are useful parameters for predicting prognosis based on tumor invasion and metastasis [23,66]. Further, SR sFas levels are a possible predictor of cancer risk before diagnosis [38]. sFasL levels in pleural fluid can discriminate malignant pleural effusion (PE) from non-malignant PE [67]. In addition, a significant increase in SR sFasL levels may be related to benzodiazepine-associated carcinogenesis in over-weight patients [68].

Table 1. Possible usage of sFas, sFasL, and DcR3 as clinical biomarkers in cancers.

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, breast cancer (BRC), (primary and recurrent)	Serum (SR) sFas levels in patients with BRC were significantly higher than those in healthy controls (HC). SR sFas levels were elevated in recurrent patients (REC), especially in those with liver metastasis. Patients with higher SR sFas levels had a worse prognosis among primary patients (PRI). SR sFas levels in patients with PRI-BRC may be useful as an independent prognostic indicator for overall and disease-free survival after surgery.	P: 233 (total BRC) [all f; (Rg: 30–88, Mn: 55.1)], 162 (total PRI), 18 [sFas > 75 percentile (H-sFas)], 144 [sFas < 75 percentile (L-sFas)], 71 (total REC), [metastatic sites: 16 liver (LIV), 22 lung, 6 brain, 39, bone, 43 soft tissues], C: 118 (HC) [59 m/59 f; (nd, nd)]	SR (sFas, ng/ml), ELISA (Md, Iqr); [BRC-PRI (0.815, 0.590–1.200)], [total BRC-REC (1.510, 1.140–2.263)], [total HC (1.135, 0.150–2.000)], [BRC-REC: LIV (2.710, 1.340–3.440), non-LIV (1,430, 1.140–2.040)], [HC: f (0.580, 0.150–1.380), m (1.760, 0.705–2.440)]; $p = 0.024$ (BRC-PRI vs HC-f); $p < 0.001$ (BRC-REC vs HC-f), $p = 0.010$ (BRC-REC: LIV vs non-LIV), log-rank test for survival (BRC-PRI: H-sFas vs L-sFas): $p = 0.013$ (overall), $p = 0.032$ (disease-free)	[14]
sFas, lymphoma (LYM) (non-Hodgkin's, aggressive)	Serum (SR) sFas levels in patients with aggressive non-Hodgkin's (NH)-LYM, especially in those with B symptom (BS), were significantly higher than those in healthy controls (HC). SR sFas levels might be associated with clinical symptoms and prognosis, and may help physicians in generating a therapeutic plan.	P (total NH-LYM): 67 [53 m/14 f; (Md: 62, Rg: 14–91, Mn: 59.9, SD: 15.8); 40 [with BS (BS)], 27 (non-BS); 59 [B-cell lymphoma (BCL)], 8 [T-cell lymphoma (TCL)]; 16 [stage I or II (S-I/II)], 51 [stage III or IV (S-III/IV)], C: 36 (HC) [23 m/13 f; (60, 18–78, nd, nd)]	SR (sFas, μg/l), ELISA (Mn, SD): [total NH-LYM (3.90, 1.72)], [HC (2.25, 0.72)], [NH-LYM: BS (4.20, 2.12), non-BS (2.66, 1.08); BCL (3.14, 1.52), TCL (4.56, 3.14); S-I/II (2.52, 0.98), S-III/IV (3.51, 1.86)]; $p <$ 0.005 (total NH-LYM vs HC; NH-LYM: BS vs non-BS), p = ns (NH-LYM: BCL vs TCL; NH-LYM: S-I/II vs S-III/IV)	[15]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, gynecological cancer (GYC) [cervical cancer (CEC), endometrial cancer (ENC), and ovarian cancer (OVC)]	Serum (SR) sFas levels in patients with advanced stages (stage III/IV), but not always lower stages (stage I/II) GYC, were significantly higher than those in healthy controls (HC), irrespective of the type of GYC. SR sFas levels in patients with advanced metastatic GYC exceeded those in patients with localized cancer. No death occurred in patients with CEC or ENC with SR sFas level < 1.5 ng/ml. Upper or lower SR sFas levels set to 1.5 ng/ml was a statistically significant survival factor in CEC and OVC, but not in ENC.	P: 28 (total CEC) [all f; (47.2, 13.5)], 23 [stage I or II (S-I/II)], 5 [stage III/IV (S-III/IV)], 18 (total ENC) [all f; (55.0, 13.9)] 12 (S-I/II), 6 (S-III/IV), 18 (total OVC) [all f; (52.4, 9.8)], 4 (S-I/II), 14 (S-III/IV), C: 24 (HC) [all f, (40.5, 6.9)]	SR (sFas, ng/ml), ELISA (Mn, SD): [total CEC: total (1.877, 1.678)], [total ENC: total (1.661, 0.499)], [total OVC: (1.660, 0.609)], [HC (0.944, 0.262)], [CEC: S-I/II (1.436, 0.298), S-III/IV (3.906, 3.501)], [ENC: S-I/II (1.418, 0.322), S-III/IV (2.146, 0.442)], [OVC: S-I/II (1.215, 0.124), SIII/IV (1.723, 0.647)]; $p < 0.0001$ (CEC-S-III/IV vs CEC-S-I/II, HC; ENC-S-III/IV, ENC-S-I/II vs HC; OVC-S-III/IV vs HC, $p = 0.1747$ (CEC-S-I/II vs HC), $p = 0.0004$ (ENC-S-III/IV vs ENC-S-I/II), log-rank test for survival (sFas in ng/ml: >1.5 vs < 1.5): $p = 0.001$ (CEC), $p = 0.128$ (ENC), $p = 0.012$ (OVC)	[16]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFasL, gastric cancer (GAC) (primary)	Serum (SR) sFasL levels in patients with GAC were not significantly different from those in healthy controls (HC). However, SR sFasL levels in patients with GAC increased reflective of disease stages, and the patients with high SR sFasL levels had the worst prognosis. SR sFasL levels could not be a marker for the early detection of GAC, but a prognostic marker for assessing the progression of advanced GAC.	P: 166 (total GAC) [111 m/55 f; (Rg: 34–84, Mn: 63.0)], 40 [stage 0 (S-0)), 61 [stage IA, IB (S-I)], 25 [stage II (S-II)], 28 [stage IIIA, IIIB (S-III)], 12 [stage IV (S-IV)]; 33 [sFasL > 0.08 ng/ml (H-sFasL)], 133 [sFasL < 0.08 ng/ml (L-sFasL)], C: 43 (HC) [32 m/11 f; (34–79, 61.9)]	SR (sFasL, ng/ml), ELISA (Md, Iqr): [total GAC (0.04, 0.02–0.08)], [HC (0.03, 0.02–0.06)], [GAC: S-0 (0.03, 0.01–0.06), S-I (0.03, 0.01–0.06), S-II (0.03, 0.01–0.06), S-III (0.17, 0.09–0.22), S-IV (1.69, 0.35–2.95)]; $p = 0.738$ (total GAC vs HC), $p < 0.001$ (S-III vs HC, S-0; S-IV vs S-I), $p = 0.02$ (S-III vs S-II), $p < 0.078$ (S-II vs HC), $p = 0.67$ (S-I vs HC), log-rank test for survival (H-sFasL vs L-sFasL): $p < 0.001$	[17]
sFasL, bladder cancer (BLC) (primary)	Serum (SR) sFasL levels in patients with BLC were significantly higher than those in healthy controls (HC) and positively correlated with both histologic disease progression as well as advancement in the tumor grade. Elevated SR sFasL levels may be associated with a greater risk of disease progression and recurrence in patients with BLC.	P: 163 (total BLC) [132 m/31 f; (Rg: 24–89)], histologic stage: 85 (Ta), 43 (T1), 8 (Tis), 136 (Ta+T1+Tis), 27 (T2-4), tumor grade (TNM): 52 [grade 1 (G1)], 58 (G2), 53 (G3), C: 24 (HC) [nd/nd; (nd)]	SR (sFasL, ng/ml), ELISA (Mn, SD): [total BLC (0.18, 0.18)], [HC (0.07, 0.09)], [BLC: Ta (0.10, 0.09), T1 (0.20, 0.15), Tis (0.27, 0.26), Ta+T1+Tis (0.14, 0.14)], T2-4 (0.35, 0.26); G1 (0.11, 0.11), G2 (0.15, 0.16), G3 (0.26. 0.22)]; $p < 0.05$ (total BLC vs HC; Ta vs T1, Tis; T2-4 vs Ta+T1+Tis; G3 vs G1, G2)	[18]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, melanoma (MEL)	Serum (SR) sFas levels in patients with MEL were significantly higher than those in healthy controls (HC). Elevated SR sFas levels were strongly associated with poor overall and progression-free survival in patients with MEL.	P: 125 (total MEL), 31 [stage I/II (S-I/II)] [14 m/17 f; m (52.8, 2.8)/f (51.3, 3.3)], 46 (S-III) [19 m/27 f; m (55.7, 2.3)/f (56.1, 3.0)], 48 (S-IV) [30 m/18 f; m (60.2, 1.7)/f (56.3, 2.5)], C: 30 (HC) [15 m/15 f; m (54, 5.3)/f (52, 7.5)]	SR (sFas, ng/ml), ELISA (Mn, SEM): [MEL: SI/II (7.61, 0.38), SIII (8.51, 0.46), SIV (9.32, 0.43)], [HC (6.27, 0.25)]; $p < 0.0005$ (total MEL vs HC); $p < 0.05$ (among SI/II, SIII, SIV), log rank test for survival (sFas in ng/ml: <7.92 vs >7.92), $p = 0.0002$ (overall), $p = 0.0047$ (progression-free)	[19]
sFasL, head and neck cancer (HNC) (squamous cell)	Serum (SR) sFasL levels in patients with active disease (AD) HNC were significantly lower than those in patients who appeared tumor-free (TF) after surgery. SR sFasL levels in HNC-TF patients were comparable to those in healthy controls (HC).	P: 37 (total HNC), [20 m/17 f; (Mn: 60, SD: 13)], 18 (TF), 19 (AD), C: 35(HC) [18 m/17 f; (56, 16)]	SR (sFasL, ng/ml), ELISA (Md, Iqr): [HNC: AD (ca. 0.43, ca. 0.22-ca. 0.56), TF (ca. 0.62, ca. 0.41-ca. 0.90)], [HC (ca. 0.67, ca. 0.22-ca. 0.56)]; $p = 0.0183$ (HNC: AD vs TF), $p = 0.8283$ (HNC-TF vs HC)	[20]
sFas, ovarian cancer (OVC) (primary, invasive)	Serum (SR) sFas levels in patients with OVC were not significantly different from healthy controls (HC). Patients with the highest tertile in SR sFas level were not at significantly increased risk of OVC, compared to patients with the lowest sFas tertile.	P: 138 (total OVC) (3 cohorts nested) [all f; (Mn: 53.8, SD: 8.8)], C: 263 (HC) [all f; (53.8, 8.8)]	SR (sFas, ng/ml), ELISA (Mn, SD): [total OVC (7.2, 4.6)], [HC (7.1, 2.2)]; $p = 0.51$ (total OVC vs HC), risk analysis for OVC (sFas tertiles): p for trend = 0.71, OR = 0.87 (95% CI: 0.42–1.82) (highest vs lowest, adjusted for potential confounders)	[21]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, breast cancer (BRC) (invasive)	Serum (SR) sFas levels in patients with BRC were significantly higher than those in benign breast tumor controls (BBT). SR sFas levels in older patients with BRC and those with more advanced tumor stage were significantly higher than those in younger patients and those with less advanced stage, respectively. SR sFas levels may reflect the disease severity in invasive BRC defined by TNM staging as an independent factor.	P: 57 (total BRC) [all f; (Mn: 51, Rg: 32–79)], 27 [age < 50 (YNG)], 30 [age ≥ 50 (OLD)]; tumor stage: 5 [TNM stage I (S-I)], 34 (S-II), 18 (S-III), C: 12 (BBT) [all f; (nd, nd)] (6 fibrocystic disease, 6 fibroadenoma)	SR (sFas, pg/ml), ELISA (Mn, SD): [total BRC (794.2, 183.0)], [BBT (582.1, 62.8)], [BRC: YNG (735.4, 150.2), OLD (847.2, 195.7); S-I (646.4, 110.5), S-II (772.1, 156.9), S-III (877.1, 212.0)]; $p < 0.001$ (total BRC vs BBT), $p = 0.020$ (BRC: YNG vs OLD), $p = 0.021$ (BRC: among SI, SII, SIII), multivariate analysis for sFas: $p = 0.005$ (TNM stage)	[22]
DcR3, various cancers (gastric, liver, pancreatic, gallbladder, colon, thyroid, lung, bone, breast, and larynx)	Serum (SR) DcR3 levels were positive in 56.2% of patients with various cancers. Almost all (98.8%) SR DcR3 positive individuals had malignancy, excluding liver cirrhosis (LCI) cases. In contrast, 97.9% of healthy controls (HC) and patients with acute infection were SR DcR3 negative. In patients with gastric cancer (GAC), SR DcR3 levels significantly depended on the tumor node and metastasis status. SR DcR3 levels were considered as a novel parameter for diagnosis, treatment, and prognosis of malignancies.	P: 146 (total MT) [nd/nd, (nd)], 31 (total GAC), tumor invasion and metastasis (TNM classification): 15 (T1-T2), 16 (T3-T4); 19 (N0-N1), 12 (N2-N3); 21 (M0), 10 (M1); 13 (≤T2/N1/M0), 18 (>T2/N1/M0), 35 (liver), 21 (pancreatic), 12 (gallbladder), 11 (colon), 13 (thyroid), 3 (bone), 10 (lung), 5 (breast), 5 (larynx), C: 53 (total non-MT) [nd/nd (nd)], 19 (cholecystitis or appendicitis), 5 (LCI), 29 (HC)	SR (DcR3, pg/ml), ELISA (Md): [total MT (55)], [MT: total GAC (52), liver (35), pancreatic (<10), gallbladder (28), colon (45), thyroid (23), lung (< 10), bone (50), breast (< 10), larynx (< 10)], [LCI (45)], [HC (< 10)], [GAC: T1-T2 (30), T3-T4 (60); N0-N1 (30), N2-N3 (95); M0 (40), M1 (95); ≤T2/N1/M0 (24), >T2/N1/M0 (110)]: $p = 0.202$ (GAC: T1-T2 vs T3-T4), $p = 0.043$ (GAC: N0-N1 vs N2-N3), $p = 0.039$ (GAC: M0 vs M1), $p < 0.004$ (GAC: ≤T2/N1/M0 vs >T2/N1/M0)	[23]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas and sFasL, lung cancer (LUC)	Although statistically insignificant, bronchoalveolar lavage fluid (BLF) sFas and sFasL levels in patients with LUC were higher than those in healthy controls (HC).	P: 27 (LUC) [all m; (Md: 62.9, SD: 10.7)], C: 25 (HC) [14 m/11 f (47.9, 13.9)]	BLF (sFas/sFasL, pg/ml), ELISA (Mn, SD): [LUC (60.8/51.6, 56.8/39.2)], [HC (39.5/41.2, 25.9/27.4)]; p = 0.349/0.341 (LUC vs HC)	[24]
sFas and sFasL, colorectal cancer (CRC) (advanced)	An increment of serum (SR) sFas/sFasL ratio could be an excellent chemosensitivity marker in patients with advanced CRC after oxaliplatin-5-fluorouracil (OXP-5FU) treatment. A decreased ratio after treatment can be a chemoresistance predictor despite an initial response. SR sFas/sFasL ratio may be useful as a dynamic response predictor in patients with CRC following chemotherapy.	P: 68 (total CRC) [42 m/26 f; (Md: 63, Rg: 33–80)], measurement time-points: basal (BS, n = 68), 3 months (3M, n = 46), 6 months (6M, n = 26), and 9/12 months (9/12M, n = 20) after OXP-5FU treatment, response after chemotherapy: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)	SR (sFas/sFasL, ng/ml), ELISA (Mn, Rg): [CRC: BS (10.02/0.14, 2.9–100/0.01–1.25), 3M (13.2/0.07, 5.7–100/0.01–0.39), 6M (11.9/0.11, 3.5–22.3/0.01–0.46), 9/12M (10.3/0.26, 6.1–16.7/0.01–1.25)], sFas/sFasL: [CR/PR (14.2, 0.06–188.4), SD/PD (2.29, 0.02–29.2)]; p = 0.0001 (sFas: 3M vs BS); p = 0.007 (sFasL: 6M vs BS); p = 0.003 (sFasL: 9/12M vs BS), p = 0.005 (sFas/sFasL ratio: CR/PR vs SD/PD)	[25]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas and sFasL, lung cancer (LUC) [small cell (SC)]	Serum (SR) sFas and sFasL levels in SC-LUC patients were significantly higher than those in healthy controls (HC). SR sFas levels may be an important marker of tumorigenesis and metastasis in SC-LUC. SR sFas levels may predict response to chemotherapy in patients with SC-LUC.	P: 21 (total SC-LUC) [15 m/6 f; (Mn: 65.7, Rg: 47–81)], 8 [limited disease (LIM)], 13 [extended disease (EXT)]; 11 [with distant metastasis (DM)], 10 (non-DM); 7 [complete response (CR)], 14 [partial response (PR)/no change (NC)/progressive disease (PD)], C: 12 (HC) [8 m/4 f (Mn: 63.8, Rg: 50–78)]	SR (sFas/sFasL, ng/ml), ELISA (Mn, SEM): [total SC-LUC (4.72/0.56, 0.27/0.06)], [HC (1.98/0.27, 0.12/0.09)], [SC-LUC: LIM (4.05/0.44, 0.33/0.14), EXT (5.14/0.64, 0.34/0.05); DM (5.26/0.70, 0.40/0.03, non-DM (4.13/0.42, 0.27/0.12); CR (3.58/0.50, 0.19/0.15), PR/NC/PD (5.29/0.59, 0.29/0.07)]; $p < 0.001$/$p < 0.001$ (SC-LUC: total, EXT, DM, CR, PR/NC/PD vs HC), sFas: $p < 0.001$ (SC-LUC: LIM, non-DM vs HC; SC-LUC: EXT vs LIM; DM vs non-DM; CR vs PR/NC/PD)	[26]
sFasL, stomach cancer (STC)	Serum (SR) sFasL levels did not consistently predict the future risk of the disease, however, SR sFasL levels in female patients with STC were significantly higher than those in non-STC controls. No statistically significant difference in SR sFasL level was observed between *H. pylori*-positive (HP) and HP-negative (non-HP) for both patients with STC and non-STC controls, irrespective of the gender.	P: 210 (total STC) [110 m (109 m for sFasL)/100 f; (Mn: 63.7/61.6, SD: 7.9/8.2)], 96 m/91 f (HP), 14 m/9 f (non-HP), C: 410 (total non-STC) [212 m (211 m for sFasL)/198 f; (63.4/61.5, 7.9/8.3)], 170 m/157 f (HP), 42 m/41 f (non-HP)	SR [sFasL (m/f), pg/ml], ELISA (Mn, SD): [total STC (2.26/2.22, 1.15/0.85)], [STC: HP-p (2.23/2.27, 1.18/0.81), non-HP (2.26/2.21, 1.15/0.86)], [total non-STC (2.20/2.04, 0.76/0.79)], [non-STC: HP (2.21/2.10, 0.92/0.83), non-HP (2.27/2.07, 0.81/0.75)]; $p = 0.38$/$p = 0.013$ (total STC vs total non-STC), $p = 0.90$/$p = 0.56$ (STC: HP vs non-HP), $p = 0.091$/$p = 0.88$ (non-STC: HP vs non-HP)	[27]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFasL, uterine cancer (UTC) [cervical (CEC), endometrial (ENC)]	Serum (SR) sFasL levels in patients with UTC with high levels of a UTC-biomarker, receptor-binding cancer antigen expressed on SiSo cells (RCAS1), were not significantly different from those in healthy controls (HC).	P: 113 (total UTC, RCAS1 ≥10 U/ml), 63 (CEC), 50 (ENC), [all f; CEC/ENC (Mn: 51/56, SD: 16/11)], C: 54 (HC) [all f; (Mn: 36, Rg: 21–69)]	SR (sFasL, ng/ml), ELISA (Mn, SD): [total UTC (0.05, 0.01)], [HC (0.06, 0.01)]; p = ns (total UTC vs HC)	[28]
sFas, bladder cancer (BLC) (non-muscle-invasive transitional)	Higher urine (UR) levels of sFas in patients with superficial BLC were associated with the presence, characteristics, and aggressiveness of the tumor. UR sFas level was a promising biomarker for the detection of BLC. UR sFas level was an independent predictor of the presence and invasiveness in patients with BLC.	P: 122 (BLC) [88 m/34 f; (Md: 73.1, Rg: 40.2–94.2)], C: 107 (non-BLC) [65 m/42 f (69.9, 21.0–86.3)], 10 [healthy controls (HC)] [nd, (nd, nd)]	UR (sFas, ng/ml), ELISA (Md, Iqr): [BLC (129.5, 206.6)], [non-BLC (43.4, 73.2)]; p < 0.001 (BLC vs non-BLC), risk analysis for BLC (sFas): p = 0.001, OR = 3.072 (95% CI: 1.606–5.876) (presence), p = 0.016, OR = 3.691 (95% CI: 1.275–10.686) (invasive tumor)	[29]
sFasL, testicular germ cell tumor (TGCT)	No significant differences in serum (SR) sFasL levels were observed between patients with total TGCT and healthy controls (HC). SR sFasL was not a suitable marker for detecting TGCT.	P: 19 (total TGCT) [all m; (Rg: 24–55)], 15 [seminomatous tumors (ST)], 4 (non-ST), C: 6 (HC) [all m; (age-matched)]	SR (sFasL, ng/ml), ELISA (Rg): [TGCT-ST, TGCT-non-ST, and HC (ca. 0.05–ca. 0.09)]; p = ns (TGCT-ST vs HC, TGCT-non-ST; TGCT-non-ST vs HC)	[30]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
DcR3, ovarian cancer (OVC)	Serum (SR) DcR3 levels in patients with OVC were significantly higher than those in surgically normal (SN), benign diseases (BN), and healthy controls (HC). SR DcR3 levels were a new marker for OVC diagnosis, and may improve early detection of OVC when used in combination with traditional diagnostic tests such as CA125.	P: 67 (total OVC), [all f; (nd)], 34 [serous (SER)], 33 (non-SER); tumor stage: 16 [early stages (S-I/II)], 51 [late stages (S-III/IV)], C: 108 (total non-OVC) [all f; (nd)], 43 (SN), 24 (BN), 41 (HC)	SR (DcR3, ng/ml), ELISA (Mn, SD): [total OVC (1.42, 0.96)], [SN (0.84, 0.59)], [BN (0.86, 0.76)], [HC (1.62, 5.1)], [SN/HC (1.22, 3.58)], [OVC: SER (1.31, 1.11), non-SER (1.54, 0.78); S-I/II (1.21, 0.89), S-III/IV (1.49, 0.99)]; $p = 0.0019$ (total OVC vs HC), $p = 0.00003$ (total OVC vs SN/HC), $p = 0.000007$ (total OVC vs total non-OVC), ROC-curve analysis for OVC diagnosis: AUC = 0.71 (DcR3), AUC = 0.87 (CA125)	[31]
sFas, cervical cancer (CEC) [cervical intraepithelial neoplasia grade I (CIN-I) and squamous cell (SQ)]	Serum (SR) sFas levels in patients with CEC with mild dysplasia, CIN-I, and SQ grades were significantly higher than those in healthy controls (HC). No statistically significant difference in SR sFas levels was observed between CIN-I and SQ. SR sFas levels could help the prognosis and treatment of patients with precancerous lesions or CEC.	P: 43 (total CEC), 21 (CIN-I) [all f; (Rg: 22–55)], 22 (SQ) [all f; (30–83)], C: 20 (HC): [all f; (22–46)]	SR (sFas, ng/ml), ELISA (Md, Iqr): [CEC: CIN-I (ca. 2.0, ca. 1.6–ca. 2.6), SQ (ca. 2.3, ca. 1.7–ca. 3.3)], [HC (ca. 1.1, ca. 1.0–ca. 1.5)]; $p = 0.007$ (CEC-CIN-I vs HC), $p \leq 0.001$ (CEC-SQ vs HC), $p = 0.331$ (CEC: CIN I vs SQ)	[32]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, ovarian cancer (OVC) (epithelial)	Patients with primary chemo-resistant (CR) OVC showed significantly higher serum (SR) post-operative (sFas2) levels than those of patients graded as chemo-sensitive (CS), and had a sFas2/pre-operative (sFas1) ratio of ≥1. SR sFas2/sFas1 ratio was a significant indicator for the prediction of response to chemotherapy. SR sFas2/sFas1 ratio and mid-chemotherapy (sFas3)/sFas1 ratio were significantly higher in patients with evidence of disease (ED) after chemotherapy than those in non-ED patients. SR sFas levels were a useful biomarker for predicting the response to platinum-based chemotherapy in patients with epithelial OVC.	P: 35 (total OVC) [all f; (Rg: 26–6124)], 24 [primary chemo-sensitive (CS)], 11 [primary chemo-resistant (CR)], 20 [ED after chemotherapy (ED)], 15 (non-ED), measurement time-points: pre-operative (sFas1), post-operative (sFas2), mid-chemotherapy (sFas3), post-chemotherapy (sFas4)	SR (sFas, ng/ml), ELISA (Mn, SD) (sFas1/sFas2/sFas3/sFas4); [OVC: CS (2.64, 0.91)/(2.11, 0.88)/(3.54, 1.42)/(3.06, 1.46), CR (2.29, 1.06)/(3.11, 1.27)/(3.72, 1.86)/(2.89, 1.56), ED (2.35, 0.97)/(2.57, 1.26)/(3.92, 1.72)/(3.23, 1.69), non-ED (2.77, 0.92)/(2.23, 0.87)/(3.17, 1.21)/(2.70, 1.09)]], sFas2/sFas1 ratio: CS (0.80, 0.17), CR (1.43, 0.50)]; p = 0.214/p = 0.033/p = 0.736/p = 0.859 (CS vs CR), sFas2/sFas1 ratio: p = 0.001 (CS vs CR), ED vs non-ED: p = 0.018 (sFas2/sFas1 ratio), p = 0.028 (sFas3/sFas1 ratio)	[33]
DcR3, ovarian cancer (OVC) (epithelial)	High DcR3 ascites (AS) levels in patients with OVC were associated with a significantly higher incidence of platinum-drug treatment-resistant disease. Patients with higher AS DcR3 levels showed a non-significant shorter progression-free and overall survival.	P: 44 (total OVC, stage III-C/IV), 22 [high (≥ median) DcR3 (H-DcR3)] [all f; (Mn:64, SD:12)], 22 [low DcR3 (< median) (L-DcR3)] [all f; (60, 12)]	AS (DcR3, pg/ml), ELISA (Mn, SD, Rg): [total OVC (5537, 3581, 77–13092)]; platinum-drug treatment sensitivity: p = 0.04 (H-DcR3 vs L-DcR3), log rank test for survival (H-DcR3 vs L-DcR3): p = 0.14 (progression-free), p = 0.12 (overall)	[34]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFasL, esophageal cancer (ESC) (adenocarcinoma)	Serum (SR) sFasL levels were a marker with the highest sensitivity and specificity for discriminating patients with ESC from gastro-esophageal reflux (GERD) controls among 53 cancer-related proteins examined.	P: 18 (ESC) [all m; (Mn: 58.9)], C: 14 (GERD) [all m; (58.2)]	SR (sFasL, arbitrary unit), MPAA [number of samples above average intensity (ca. 42)]: 0/14 (ESC) and 15/18 (GERD); discriminating power of sFasL (ESC from GERD): 83.3 % (sensitivity), 100% (specificity)	[35]
DcR3, renal cell cancer (RCC)	Serum (SR) DcR3 levels in patients with non-metastatic RCC at advanced tumor stages and those with metastatic RCC at any tumor stage were significantly higher than those in healthy controls (HC). SR DcR3 levels were a feasible prognostic biomarker in RCC.	P: 42 (total RCC) [nd/nd (nd)], tumor extent: 28 (T1), 2 (T2), 11 (T3), 1 (T4); regional lymph node metastasis: 39 (N0/pN0), 3 (pN1, pN2); distant metastasis: 40 (M0), 2 (M1), C: 15 (HC) [nd/nd (nd)]	SR (DcR3, ng/ml), ELISA (Rg): [RCC (0.03–10.14)], [HC (0.03–1.65)]; $p = 0.007$ (T3/T4-M0/N0 vs HC), $p = 0.001$ (all T-M1/N1 vs HC), $p = 0.7$ (T1/T2-M0/N0 vs HC)	[36]
sFasL, breast cancer (BRC) (locally advanced)	Serum (SR) sFasL levels in locally advanced BRC patients with complete or partial response (CR and PR, respectively) after neoadjuvant chemotherapy (NAC) were significantly higher than those in patients with no response (NR). SR sFasL levels may have a predictive value for treatment response in NAC.	P: 43 (total BRC, stage II-B or stage III), 27 (CR or PR), 16 (NR) [nd/nd; (nd)]	SR (sFasL, pg/ml), MPAA (Md): [CR or PR (> 32)], [NR (< 32)]; $p < 0.05$ (CR/PR vs NR)	[37]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, various cancers, [stomach (STC), colon (COC), liver (LIC), gallbladder (GBC), lung (LUC), and others]	A significant association between serum (SR) sFas levels and the mortality in patients with multiple cancers was observed in a large-scale cohort study. SR sFas levels could detect people at high risk of cancer before diagnosis, since it increased in apparently healthy control people (HC).	P: 798 [total cancers (TC)] [460 m/338 f; (Mn: 64.3, SD: 8.1)], C: 2353 (HC) [1360 m/993 f; (64.2, 8.0)], sFas level (ng/ml): <1.9 (Q1); 1.9–2.2 (Q2); 2.3-2.6 (Q3); >2.7 (Q4); body-mass-index (BMI) (mean, SD)/smoking habits (%)/drinking status (%): [total cancers (22.6, 3.0)/37.2/47.6], [HC (22.6, 3.1)/27.0/50.8]	SR (sFas, ng/ml), ELISA (Mn, SD): [TC: STC (ca. 2.6, ca. 3.0), COC (ca. 3.3, ca. 7.7), LIC (ca. 3.8, ca. 1.3), GBC (ca. 2.5, ca. 0.76), LUC (ca. 2.8, ca. 6.1)], [HC (2.41, 1.81)]; risk analysis for cancer mortality (sFas quartiles): p for trend = 0.007, OR = 1.00 (Q1), 1.17 (Q2), 1.32 (Q3), 1.81 (Q4) (adjusted for age, BMI, smoking habits, and drinking status)	[38]
DcR3, ovarian cancer (OVC)	Standardized baseline serum (SR) DcR3 levels in patients with OVC were only slightly higher than those in non-OVC controls. SR DcR3 levels in either total or serous OVC before diagnosis were indistinguishable from those in non-OVC controls.	P: 34 (OVC) [all f; (Mn: 59.0, SD: 5.7)] C: 70 (non-OVC) [all f; (59.0, 5.6)], (all were participants in the Carotene and Retinol Efficacy Trial)	SR (DcR3, nd), ELISA (Mn, SD): [OVC (0.05, 0.66)], [non-OVC (-0.01, 0.99); p = 0.76 (OVC vs non-OVC), risk analysis for cancer: p = 0.696, HR = 1.09 (95% CI: 0.71–1.68) (all OVC), p = 0.487, HR = 1.22 (95% CI: 0.69–2.15) (serous OVC)	[39]
sFas and sFasL, breast cancer (BRC)	Serum (SR) sFasL, but not sFas, levels in patients with BRC were significantly lower than those in healthy controls (HC), without a relation to the Nottingham Prognostic Index (NPI) scoring. SR sFas and sFasL levels were overall uninformative, except for the low SR sFasL levels in the group with BRC.	P: 160 (total BRC) [1 m/159 f; (Mn: 62, SD: 12)], NPI score: 58 good prognostic group (G-PG), 59 moderate PG (M-PG), 35 poor PG (P-PG), C: 63 (HC) [1 m/62 f; (60, 7)]	SR (sFas/sFasL, pg/ml), ELISA (Md, Iqr): [BRC: G-PG (1600/153, 1260–2500/100–433), M-PG (1410/146, 1120–2170/80–338), P-PG (1600/154, 960–2250/84–435)], [HC (1635/182, 1023–2643/114–1128); p = ns/p < 0.05 (total BRC vs HC), p = 0.70/0.26 (among G-PG, M-PG, P-PG, HC)	[40]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas and sFasL, breast cancer (BRC), and prostate cancer (PRC)	Regardless of age, serum (SR) sFas levels and SR sFasL levels in patients with either BRC or PRC were significantly higher and lower, respectively, than those in healthy controls (HC). SR sFas and SR sFasL levels exhibited increasing and decreasing trends, respectively, concerning disease severity defined by tumor stages in both patients with BRC and PRC.	P: 66 (total BRC) (all f; Mn: 62, SD: 14)], tumor stage (TNM): 11 [stage I (SI)], 23 (S-II), 24 (S-III), 8 (S-IV), 38 (total PRC) [(all m; (66, 9)], 11 (S-II), 14 (S-III), 13 (S-IV), C: 70 [HC for BRC (HC-BRC)] [all f; (age-matched)], 40 [HC for PRC (HC-PRC)] [all m; (age-matched)]	SR (sFas/sFasL, pg/ml), ELISA (Mn, SD): [BRC (5202/75.3 1732/26.2)], [HC-BRC (3585/94.4, 918/20.1)], [PRC (6249/69.7, 2324/22.0, 5587/62.2)], [HC-PRC (5023/89.0, 1309/19.6)]; $p < 0.001$/$p < 0.0001$ (BRC: total vs HC), $p < 0.05$/$p < 0.0001$ (PRC: total vs HC), $p < 0.005$ (sFas in BRC: S-II, S-III, S-IV vs HC; S-I vs S-III; S-II, S-III vs S-IV; sFas in PRC: S-IV vs HC; sFasL in BRC: S-II, S-III, S-IV vs HC, S-I vs S-IV; sFasL in PRC: S-III, S-IV vs HC), $p < 0.05$ (sFas in BRC: S-I vs S-IV; S-II vs S-III; sFas in PRC: S-II vs S-IV; sFasL in BRC: S-I vs S-II, S-III; sFasL in PRC: S-II vs HC)	[41]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, ovarian cancer (OVC)	Serum (SR) sFas levels in patients with OVC were significantly higher than those in healthy controls (HC). Higher SR sFas levels were associated with a shorter duration of relapse-free period (RFP) in patients with serous OVC (SOVC). Patients with poorly differentiated (PD) SOVC had 2-fold higher SR sFas levels than those in patients with moderately and highly differentiated (MD/HD) tumors. SR sFas levels can be an additional prognostic factor in patients with SOVC.	P: 100 (total OVC) [all f; (Rg: 28–65)], 51 (total SOVC), disease stage: 2 stage I (S-I), 3 (S-II), 32 (S-III), 14 (S-IV), RFP: 36 [<12 months (S-RFP)], 15 [≥12 months (L-RFP)], tumor differentiation: 38 (PD), 11 (MD/HD), 11 [borderline tumors (BLT)], 38 [benign ovarian tumors (BOT)], C: 60 (HC) [all f; (28–65)]	SR (sFas, ng/ml), ELISA (Mn, SEM): [total OVC (2.31, 0.61)], [HC (0.86, 0.3)], [total SOVC (2.09, 0.45)], [SOVC: S-I (1.17, 0.4), S-II (1.75, 0.4), S-III (2.03, 0.5), S-IV (2.36, 0.9); S-RFP (2.53, 0.87), L-RFP (1.84, 0.59); PD (2.53, 0.59), MD/HD (1.11, 0.18)], [BLT (3.58, 1.35)], [BOT (2.21, 0.43)]; $p = 0.003$ (total OVC vs HC)	[42]
sFas and sFasL, gastric cancer (GAC) (adenocarcinoma)	Serum (SR) sFas levels were significantly higher in patients with GAC than those in the non-GAC control group, while SR sFasL levels were significantly lower. Patients with GAC without lymph node metastasis (LNM) had significantly higher SR sFas levels than those with LNM. A significant difference in SR sFas levels was observed between patients with GAC and precancerous/non-tumoral groups. SR sFas levels may serve as a cost-effective, non-invasive tool for early diagnosis of GAC.	P: 59 (total GAC) [44 m/15 f; (Mn: 60.25, SD: 10)], disease region: 45 [intestinal (IT)], 14 [diffuse (DF)], 18 [cardia (CD)], 40 [non-cardia (NCD)], LNM status: 28 or 30 [N>0 (LNM)], 14 [N0 (non-LNM)], C: 62 (total non-GAC) [32 m/30 f; (47.32, 16)], 10 [near normal mucosa (NNM)], 34 [chronic active gastritis (CAG)], 15 [precancerous lesions (PCL)]	SR (sFas/sFasL, pg/ml), ELISA (Mn, SEM): [total GAC (305.97/0.138, 63.71/0.04)], [total non-GAC (92.98/0.150, 4.95/0.02)], [GAC: LNM (273.00/0.11, 68.97/0.03), non-LNM (404.86/0.24, 150.62/0.16)], sFas: [non-GAC: NNM (72.01, 9.78), CAG (95.75, 6.71), PCL (100.68, 9.55)]; $p < 0.001$/$p < 0.001$ (total GAC vs total non-GAC), $p = 0.044$/$p = 0.57$ (GAC: LNM vs non-LNM), sFas: $p = 0.009$ (total GAC vs PCL), $p < 0.001$ (total GAC vs NNM, CAG)	[43]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, head and neck cancer (HNC) (squamous cell)	Serum (SR) sFas levels were significantly higher in patients with HNC before surgery than those in healthy controls (HC). Higher SR sFas levels were observed in patients with more advanced tumor stages and those with less differentiated tumors, however, neither the difference among tumor stages nor that in tumor invasiveness was statistically significant. Surgical removal of tumors resulted in a substantial decrease in SR sFas level and approached the levels in HC. SR sFas levels may determine disease prognosis as a prospective biomarker.	P: 98 (HNC) [72 m/26 f; (Mn: 60, SD: 9)], 98 [before surgery (BS)], 48 [6 months after surgery (6M-AS)], tumor stage: 20 [stage I (S-I)], 22 (S-II), 35 (S-III), 21 (S-IV); tumor differentiation: [well-differentiated (WD)], [moderate-differentiated (MD)], [non-differentiated (ND)]; tumor invasiveness: [invasive (INV)], (non-INV), C: 30 (HC) [gender-matched; (59.2, 7)]	SR (sFas, pg/ml), ELISA (Mn, SD): [total HNC-BS (355.30, 124.60)], [HC (123.20, 71.34)], [HNC-BS: S-I (ca. 240, ca. 53), S-II (ca. 260, ca. 46), S-III (ca. 340, ca. 78), S-IV (ca. 350, ca. 78); WD (175.2, 76.31), MD (256.6, 91.34), ND (423.0, 72.11); INV (283.5, 23), non-INV (291.3, 34)], [HNC: 6M-AS (219.9, 91.31)]; p = 0.01 (total HNC-BS vs HC); p = 0.03 (HNC-BS: among WD, MD, ND), p = ns (HNC-BS: among S-I, S-II, S-III, S-IV; INV vs non-INV), p = 0.001 (HNC: total BS vs 6M)	[44]
sFas and sFasL, ovarian cancer (OVC) (malignant adnexal mass)	Serum (SR) sFasL, but not sFas, levels were significantly different between patients with OVC and those with benign diseases (BN) regarding adnexal ovarian masses. SR sFas and sFasL levels in patients with OVC at advanced, but not at early, stages were significantly higher and lower, respectively, than those in BN controls.	P: 264 (total OVC) [all f; (Md: 63, Rg: 48–87)], disease stage: 132 [stage I/II (S-I/II)], 132 (S-III/IV), C: 141 (BN) [all f; (63, 48–88)]	SR (sFas/sFasL, pg/ml), MPAA (Mn): [total OVC (4248/29.60)], [BN (4152/43.75)], [OVC: S-I/II (4118/36.05), S-III/IV (4890/23.80)]; p = ns/p = 0.01 (total OVC vs BN), p = ns/p = ns (OVC-S-I/II vs BN), p = 0.001/p = 0.001 (OVC-S-III/VI vs BN)	[45]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, lung cancer (LUC) [squamous cell carcinoma (SQ), adenocarcinoma (AD), and small cell carcinoma (SM)]	Serum (SR) sFas levels in patients with LUC were significantly higher than those in benign diseases (BN) and healthy controls (HC). A significant increase in SR sFas level was observed 24 h after chemotherapy. SR sFas levels before chemotherapy showed a statistically significant inverse correlation with survival time. Increased SR sFas levels may be an indicator of poor outcomes in patients with LUC.	P: 52 (total LUC) [46 m/6 f; (Mn: 59.2, SD: 9.5)], 39 (SQ), 4 (AD), 9 (SM), C: 19 (total BN) [12 m/7 f; (50.1, 11.6)], 13 (asthma), 6 (chronic obstructive lung disease), 35 (HC) [31 m/4 f; (50.5, 7.6)], measurement time-points (n = 17): before (BF) and 24 h (24H) after chemotherapy.	SR (sFas, pg/ml), ELISA (Mn, SD): [total LUC (ca. 310, ca. 30)], [total BN (<10, nd)], [HC (ca. 10, nd)], [LUC: BF (316, 188), 24H (710, 566)]; $p < 0.05$ (total LUC vs total BN, HC); $p = 0.016$ (LUC: BF vs 24H), p = ns (total BN vs HC), Corr. (vs sFas): $p < 0.001$, $r = -0.599$ (survival time)	[46]
DcR3, hepatocellular carcinoma (HCC)	Serum (SR) DcR3 levels in patients with HCC and cirrhosis (CIR) were significantly higher than those in patients with cholecystitis (CHO) and healthy controls (HC). SR DcR3 levels in patients with advanced tumor stage, para-cirrhosis, tumor capsular infiltration, and metastasis/recurrence (M/R) were significantly higher than those without them. SR DcR3 levels may serve as a valuable indicator in early diagnosis and contribute to predicting the clinical outcome in patients with HCC.	P: 67 (HCC) [58 m/9 f; (Mn: 48, Rg: 29–74)], tumor stage (TNM): 26 stage I (S-I), 11 (S-II), 19 (S-III), 11 (S-IV); M/R status: 40 [with M/R (M/R)], 27 (non-M/R), C: 8 (CIR) [6 m/2 f; (44, 28–60)], 17 (CHO) [9 m/8 f; (55, 25–79)], 28 (HC) [nd/nd; (nd, nd)]	SR (DcR3, pg/ml), ELISA (Mn, SD): [total HCC (197.07, 90.34)], [CIR (179.81, 102.74)], [CHO (101.59, 24.51)], [HC (96.69, 16.05)], [HCC: S-I/S-II (160.76, 62.57), S-III/S-IV (224.78, 98.85); M/R (215.04, 93.63), non-M/R (164.88, 75.66)]; $p = 0.094$ (total HCC vs CIR), $p = 0.002$ (total HCC vs CHO), $p = 0.005$ (total HCC vs HC), $p = 0.083$ (CIR vs CHO), $p = 0.003$ (CIR vs HC), $p = 0.102$ (CHO vs HC), $p = 0.014$ (HCC: SI/SII vs SIII/SIV), $p = 0.02$ (HCC: M/R vs non-M/R)	[47]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, hepatocellular carcinoma (HCC)	Serum (SR) sFas levels in HCC patients and patients with chronic liver disease (CLD) were significantly higher than those in healthy controls (HC). A significant correlation of SR sFas levels was observed with soluble tumor necrosis factor receptor (sTNFR)-II and interleukin (IL)-2R, but not with IL-8 and hepatitis-C virus (HCV)-titer.	P: 30 (HCC) [25 m/5 f; (Mn: 60.7, SD: 8.3)], [12 m/5 f; (35.1, 11.5)], 32 (CLD) [24 m/8 f; (43.4, 8.7)], 17 [chronic hepatitis C with persistent normal alanine transferase (PNALT)], C: 9 (HC) [7 m/2 f; (50.9, 4.6)]	SR (sFas, pg/ml), ELISA (Mn, SD): [HCC (762.18, 437)], [CLD (814.94, 362)], [PNALT (605.82, 304)], [HC (316, 62.5)]; $p < 0.001$ (among HCC, CLD, PNALT, HC), $p < 0.05$ (HCC, CLD vs HC), Corr. (vs sFas): $p = 0.010$, $r = 0.276$ (sTNFR-II), $p = 0.000$, $r = 0.403$ (IL-2R), $p = 0.199$, $r = -0.139$ (IL-8), $p = 0.96$, $r = 0.006$ (log HCV titer)	[48]
sFasL, colorectal cancer (CRC) with synchronous liver metastases (SLM)	Preoperative serum (SR) sFasL level was a potential prognostic factor for recurrence-free and overall survival (RFS and OS, respectively) in patients with CRC with SLM (CRC-SLM). Low preoperative SR sFasL levels may identify a subgroup of patients with CRC-SLM that are likely to benefit from liver surgery.	P: 62 (CRC-SLM) [40 m/22 f; (Mn: 60.23, SD: 10.68)], measurement time-points: pre-operative (PRE-OP), post-operative (POS-OP)	SR (sFasL, ng/ml, PRE-OP/POS-OP), ELISA (Md, 95% CI): [CRC-SLM (0.1762/0.1643, 0.12–0.41/0.11–0.26)]; risk analysis for survival (sFasL in PRE-OP: above Md vs below Md): $p = 0.019$, HR = 2.322 (95% CI: 1.272–3.590) (recurrence-free); $p = 0.020$, HR = 2.692 (95% CI: 1.168–6.206) (overall)	[49]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, breast cancer (BRC) (locally confined and metastasized)	Serum (SR) sFas levels in patients with metastasized BRC were significantly higher than those in benign disease (BN) and healthy control (HC) groups. SR sFas levels are a low-cost and non-invasive option for the detection of BRC. SR sFas levels efficiently discriminated metastatic BRC (ME) from total non-BRC controls, and locally confined patients with BRC (LO) from those with HC.	P: 79 (total BRC), 51 (LO) (all f; Md: 46.2)] (n = 42 for sFas measurement), 28 (ME) [all f; (64.4)], C: 44 (total non-BRC), 13 (BN) [all f; (44.7)], 31 (HC) [all f; (41.9)]	SR (sFas, pg/ml), MPAA (Md, Rg): [BRC: ME (4.0, 0.5–20.5), LO (2.5, 0.3–22.2)], [BN (1.9, 0.4–5.5)], [HC (1.7, 0.5–3.6)]; $p < 0.0001$ (BRC-ME vs BRC-LO, HC), $p = 0.0014$ (BRC-ME vs BN), $p = 0.0007$ (BRC-LO vs HC), $p = 0.2009$ (BRC-LO vs BN), $p = 0.3672$ (BN vs HC), ROC curve for discrimination (sFas): AUC = 84.0 % (BRC-ME vs total non-BRC), AUC = 73.4 % (BRC-LO vs HC)	[50]
sFas, hepatocellular carcinoma (HCC)	Serum (SR) sFas levels in patients with HCC and chronic hepatitis-C (CHC) with cirrhosis (CIR) caused by hepatitis-C virus infection (HCV-I) were significantly higher than those with CHC without CIR and laparoscopic cholecystectomy (LCH) controls. However, no significant difference was observed between HCC and CHC with CIR.	P: 90 (total HCV-I) [54 m/36 f; (Mn: 48.32, SD: 7.65)], 30 (HCC), 60 (total CHC), 30 [CHC with CIR (CHC-CIR)], 30 (CHC-non-CIR), C: 10 (LCH) [7 m/3 f; (42.21, 4.54)]	SR (sFas, pg/ml), ELISA (Mn, SD): [HCV-I: HCC (762.18, 437), CHC-CIR (814.94, 362), CHC-non-CIR (238.27, 135.29)], [LCH (165.5, 45.6)]; $p < 0.01$ (HCC, total CHC vs LCH; HCC, CHC-CIR vs CHC-non-CIR), p = ns (HCC vs CHC-CIR)	[51]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas and sFasL, lung cancer (LUC) [non-small cell (NSC)]	Plasma (PL) sFas levels were identified as a biomarker with strong predictive value only for males at risk of NSC-LUC.	P: 360 (NSC-LUC) [245 m/114 f/1 unknown (u); (Rg: 38–92)], C: 180 [asthma (AS)] [67 m/112 f/1 u; (38–80)], 288 (HC) [122 m/165 f/1 u; (18–60)]	PL (sFas/sFasL, nd), MPAA (case number): distribution in the prediction of NSC-LUC vs HC using best subset of 5 markers including sFas for males (total n = 182): true positive, 116; false-positive, 0; false-negative, 0; true negative 66	[52]
sFas, bladder cancer (BLC) (transitional cell and squamous cell carcinomas) with/without bilharzia	Urine supernatant (US) sFas levels in patients with BLC were significantly higher than those with benign urological disease (BUD) and healthy controls (HC). Patients with bilharzial (BIL)-BLC, but not BIL-BUD, had significantly elevated US sFas levels compared to non-BIL. US sFas levels may be used as a novel noninvasive diagnostic marker for patients with BIL -BLC.	P: 120 (total BLC) [nd/nd; (Mn: 62, SD: 11, Rg: 25–83)], 112 (BIL), 8 (non-BIL), C: 43 (total BUD) [nd/nd; (43, 15, 21–75), 20 (BIL), 23 (non-BIL), 40 (HC) [nd/nd; (39, 8, 25–57)] (all non-BIL)	US (sFas, ng/mg of urine protein), ELISA (Mn): [total BLC (142.51)], [total BUD (55.81)], [HC (30.12)], [BLC: BIL (104.8), non-BIL (66.8)], [BUD: BIL (26.2), non-BIL (23.4)]; $p < 0.0001$ (total BLC vs total BUD, HC; total BUD vs HC; BIL-BLC vs BIL-BUD, BLC-non-BIL), p = ns (BUD: BIL vs non-BIL), ROC curve analysis (sFas, BLC: BIL vs non-BIL): $p < 0.0001$, AUC = 0.998	[53]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFasL, thyroid cancer (THC) (differentiated) with/without recurrence	Plasma (PL) sFasL levels were associated with disease recurrence in THC. Patients with THC without recurrence (THC-non-REC) had significantly higher levels of PL sFasL compared to patients with recurrence (THC-REC). PL sFasL levels may assess progression-free survival (PFS) in differentiated patients with THC.	P: 35 (total THC) [11 m/24 f; (Md: 49.4)], 6 (follicular), 28 (papillary), 1 (poorly differentiated), C: 21 [healthy controls (HC)] [nd/nd; (nd)]	PL (sFasL, pg/ml), MPAA (Mn, Iqr): [THC: REC (13.08/ca. 10-ca. 14), non-REC (18.87/ca. 13–ca. 21)], [HC (nd, nd)]; p = 0.011 (THC: REC vs non-REC), risk analysis for PFS (adjusted for other risk factors): p = 0.031, HR = 0.60 (95% CI: 0.38–0.95), log rank test for PFS (sFasL in pg/ml: <15.11 vs >15.11), p = 0.0009	[54]
sFas and sFasL, hepatocellular carcinoma (HCC)	Serum (SR) sFas and sFasL levels in patients with HCC infected with hepatitis-C virus (HCV) with high degree of cirrhosis (CIR) were significantly higher than those HCV-infected non-HCC and healthy controls (HC). Both SR sFas and sFasL levels in patients with HCC increased as the tumor stage advanced. SR sFas and sFasL levels could be used as reliable diagnostic biomarkers for HCC in patients infected with HCV.	P: 30 [total HCC] [24 m/ 6 f; (Mn: 58.9, SD: 7.434)], disease stage in Okuda staging system: [stage II (S-II)], (S-III), C: 30 [non-HCC with CIR and HCV (non-HCC)] [22 m/8 f; (55.8, 7.141)], 20 (HC) [15m/5 f (56.65, 5.194)]	SR (sFas/sFasL, pg/ml), ELISA (Mn, SD): [total HCC (2024/1551, 444.4/258.35)], [non-HCC (1481.67/1180.33, 251.36/160.44)], [HC (1031/126.1, 43.395/18.83)], [HCC: S-II (1811.9/1423, 311.94/142.18), S-III (2519/1846, 281.13/225.67)]; p < 0.0001/p < 0.0001 (total HCC vs non-HCC, HC; non-HCC vs HC), p < 0.001/p = 0.0004 (HCC: S-II vs S-III)	[55]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas, prostate cancer (PRC)	Serum (SR) sFas levels in patients with PRC were significantly lower than those in benign prostate hyperplasia (BPH) controls. SR sFas levels could distinguish PRC from BPH with high sensitivity and high specificity, suggesting its high diagnostic value.	P: 46 (PRC) [all m; (Mn: 63.5, SD: 9.7)], C: 42 (BPH) [all m; (62.1, 11.9)]	SR (sFas, ng/ml), MPAA (Md, Iqr): [PRC (ca. 0.0021, ca. 0.00016–ca. 0.00032), [BPH (ca. 0.0050, ca. 0.00042–ca. 0.00059); $p < 0.0001$ (PRC vs BPH), ROC curve analysis for distinguishing PRC from BPH (sFas): AUC = 0.943 (95% CI: 0.898–0.988)	[56]
sFasL, gastrointestinal stromal carcinoma (GIST) (metastatic)	Plasma (PL) sFasL levels in metastatic patients with GIST with hand-foot skin reaction (HFSR) were significantly higher than those in patients without HFSR and healthy controls (HC). Blister fluid (BF) sFasL levels in patients with GIST with HFSR were significantly higher than those in patients with burn (BRN). PL sFasL levels in patients with GIST with HFSR were significantly correlated with PL sunitinib (SNT) levels after the drug treatment.	P: 53 (total GIST, imatinib-resistant and then received SNT-treatment) [32 m/21 f; (nd)], 23 [with grade 1-3 HFSR (HFSR)], 30 (non-HFSR), C: 10 (BRN) [nd/nd; (nd)], 10 (HC) [nd/nd, (nd)]	BF and PL (sFasL: pg/ml, PL/BF), MPAA (Mn, SD): [GIST: HFSR (119.8/133.2, 21.0/18.98), non-HFSR (50.4/nd, 4.2/nd)], [BRN (nd/67.73, nd/10.55), [HC (53.2/nd, 3.7/nd)]; PL: $p = 0.0048$ (GIST: HFSR vs non-HFSR), $p = 0.0065$ (GIST-HFSR vs HC), BF: $p = 0.0216$ (GIST-HFSR vs BRN), Corr. ($n = 17$): $p = 0.019$, $r = 0.56$ (PL: sFas vs SNT)	[57]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFasL, breast cancer (BRC) (invasive, ductal, and lobular)	Serum (SR) sFasL levels were significantly higher in patients with BRC compared to those in healthy controls (HC). SR sFasL levels in patients after one cycle of adjuvant chemotherapy (AC) were significantly higher than those in patients before AC. SR sFasL levels may help clinicians in evaluating AC treatment efficacy in patients with BRC.	P: 60 (total BRC) [all f; (Mn: 52.5, SD: 13.42, Rg: 30–75)], tumor stage (TNM): 30 [stage II (S-II)], 30 (S-III), C (HC): 30 [all f; (age-matched)], measurement time-points: before (BE) and after (AF) 3 weeks of AC with 5-fluorouracil, epirubicin, cyclophosphamide/adriamycin / paclitaxel	SR (sFasL, pg/ml), ELISA (Mn, SD): [BRC-S-II: BE-AC (165.06, 13.90), AF-AC (310.34, 10.57)], [BRC-SIII: BE-AC (262.06, 14.79), AF-AC (435.21, 30.10)], [HC (118.92, 21.95)]; $p < 0.0001$ (BRC: S-II-BE/AF-AC, S-III-BE-/AF-AC vs HC; BRC: S-II-AF-AC, S-III-BE/AF-AC vs S-II-BE-AC; BRC: S-III-AF-AC vs S-III-BE-AC)	[58]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas and sFasL, breast cancer (BRC)	Serum (SR) sFas, but not sFasL, baseline levels in patients with advanced/metastatic stage BRC were significantly higher than those in healthy controls (HC). A significant increase in SR sFas levels and a significant decrease in SR sFasL levels were observed after chemotherapy. In patients treated with a greater cardiotoxicity, the difference (Δ) in left ventricular ejection fraction (LVEF) after chemotherapy (CT) was significantly correlated with the increase in SR sFas and decrease in SR sFasL, however, patients treated with less cardiotoxic regimen showed no significant LVEF drop. SR sFas and sFasL levels could be used as sensitive biomarkers for the detection of LVEF dysfunction in patients with BRC under cardiotoxic CT.	P: 40 (total BRC), 26 [advanced or metastatic stages IIIA/IIIB/IV (GA)] [all f; (Mn: 54.4, SD: 10.2), 14 [no residual disease after surgery, stages IIA/IIB/IIIA (GB)] [all f; (53.3, 11.7)], C: 20 (HC): [all f; (54.3, 16.6)], measurement time-points: baseline (BS), before (BE) and after (AF) CT (GA patients received a more cardiotoxic chemotherapeutic regimen with epirubicin/paclitaxel than GB patients with docetaxel/mitoxantrone)	SR (sFas/sFasL, ng/ml), ELISA (Md, Iqr) or (Mn, SEM): [BRC-BS: GA (192.9/75.1, 134.0–413.7/43.1–126.3), GB (152.9/79.0, 102.5–214.0/49.9–94.6)], [HC-BS (111.3/66.1, 92.1–131.4/50.9–77.9)], [BRC-BE-CT: GA (308.8/86.6, 65.1/12.6), GB (171.6/77.1, 22.5/33.1)], [BRC-AF-CT: GA (517.8/47.9, 91.0/8.4), GB (229.5/70.0, 25.8/32.4)]; $p < 0.001$/$p = 0.601$ (BS: among BRC-GA, BRC-GB, HC), $p < 0.001$/$p = 0.010$ (BRC-GA: BE-CT vs AF-CT), $p = 0.028$/$p = 0.021$ (BRC-GB: BE-CT vs AF-CT), Corr. (sFas/sFasL vs Δ in LVEF between BE-CT and AF-CT): $p = 0.025$/$p = 0.004$, $r = -0.438$/$r_s = 0.549$ (GA), $p = 0.338$/$p = 0.276$, $r = -0.277$/$r = 0.313$ (GB)	[59]
DcR3, colorectal cancer (CRC)	Serum (SR) DcR3 levels in patients with CRC were significantly higher than those in healthy controls (HC). SR DcR3 levels obtained using LC-MSI MS were in fair correlation with those from ELISA measurements.	P: 19 (total CRC) [10 m/9 f; (Md: 56.8, Rg: 22–87)], UICC pathological stage: 9 (stage I/II), 9 (stage III/IV), 3 (HC) [nd/nd; (nd, nd)]	SR (DcR3, fmol/ml), LC-ESI MS (Mn, SD): [total CRC (116.94, 57.37)], [HC (27.23, 2.49)]; $p = 1.86 \times 10^{-9}$ (total CRC vs HC), Corr.: $p = 0.049$, $r = 0.46$ (LC-ESI MS vs ELISA)	[60]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
DcR3, hepatocellular carcinoma (HCC)	Serum (SR) DcR3 levels were significantly higher in patients with HCC and decompensated cirrhosis (DC) than those in patients with chronic viral hepatitis (CVH) and healthy controls (HC). SR DcR3 levels positively correlated with the severity of hepatic impairment, and may serve as a marker for liver fibrosis severity and disease progression.	P: 21 (HCC) [20 m/1 f; (Mn: 61.3, SD: 9.9, Rg: 50–77)], C: 46 (DC) [35 m/11 f; (64.9, 11.0, 46–89)], 58 (CVH) [40 m/18 f; (43.9, 12.7, 25–68)], 48 (HC) (age- and gender-matched)	SR (DcR3, ng/ml), ELISA (Md, Rg): [HCC (5.7, 0.6–63.8)], [DC (4.5, 0.9–61.8)], [CVH (1.1, 0-4.2)], [HC (0.8, 0–7.9); $p < 0.001$ (HCC, DC vs CVH, HC), $p = 0.006$ (CVH vs HC)	[61]
DcR3, colorectal cancer (CRC)	Serum (SR) DcR3 levels in patients with CRC were significantly higher than those in healthy controls (HC). Higher than median level (Md) of SR DcR3 was associated with multiple disease severity indices, including lymph node metastasis (LNM), distant metastasis (DM), and tumor stage. SR DcR3 levels may serve as a new tumor biomarker in the diagnosis and prognosis assessment of CRC.	P: 78 (total CRC) [43 m/35 f; 31 (< age 60), 47 (≥ age 60)], disease severity indices: 27 [with LNM (LNM)], 51 (non-LNM); 19 [with DM (DM)], 59 (non-DM); 37 [stages I/II (S-I/II)], 41 (S-III/IV), C (HC): 60 [nd/nd; (nd)]	SR (DcR3, relative value), WB (Mn, SD): [total CRC (ca. 2.4, ca. 0.7)], [HC (ca. 1.0, ca. 0.3)]; $p < 0.05$ (total CRC vs HC), $p = 0.000$ (LNM), $p = 0.018$ (DM), $p = 0.013$ (S-III/IV) (DcR3: > Md vs < Md in total CRC), ROC curve analysis: $p < 0.05$, AUC = 0.912 (95% CI: 0.857–0.963)	[62]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas and sFasL, colorectal cancer (CRC)	Serum (SR) sFas, but not sFasL, levels in patients with CRC were significantly higher than those in healthy controls (HC). The differences in both SR sFas and sFasL levels were not statistically significant between patients with CRC and those with benign colorectal diseases (BN). SR sFas, but not sFasL, levels discriminated between metastatic and non-metastatic CRC subgroups.	P: 35 (total CRC) [22 m/13 f; (Md: 69.4, Rg: 19.6–86.3)], 23 (colon) [13 m/10 f; (68.0, 19.6–80.0)], 12 (rectum) [9 m/3 f; (69.9, 46.0–86.3)], disease state: 21 [with metastasis (MET)], 14 (non-MET), C: 20 (BN) [8 m/12 f; (54.7, 24.2–89.8)], 51 (HC) [15 m/36 f; (39.4, 20.1–78.1)]	SR (sFas/sFasL, sFas: ng/ml, sFasL: pg/ml), MPAA (Md, Rg): [total CRC (3.0/50.0, 1.4–5.4/50.0–88.7)], [BN (2.5/50.0, 1.7–6.0/50.0–111.2)], [HC (1.8/50.0, 0.8–15.3/50.0–178.8)]; $p < 0.001$/p = ns (CRC vs HC), p = ns/p = ns (CRC vs BN), discriminative power: p = 0.0007/p = 0.4483 (CRC: MET vs non-MET)	[63]
sFas and sFasL, breast cancer (BRC)	Serum (SR) sFas, but not sFasL, levels in patient with BRC were significantly higher than those in healthy controls (HC). Neither SR sFas nor SR sFasL levels were significantly different between patients with BRC and those with benign breast diseases (BN). Patients with precancerous lesions, ductal carcinoma *in situ* (DCIS), as well as patients with BN could be discriminated from HC using SR sFas levels. Higher SR sFas levels was found in patients with BRC with advanced stages, particularly stage IV. SR sFas levels may serve as biomarkers during the early detection of malignant lesions.	P: 77 (total BRC) [all f; (Md: 58.7, Rg: 36.4–85.4)], tumor stages: 31 [UICC stage I (S-I)], 25 (S-II), 12 (S-III), 9 (S-IV), C: 10 (DCIS) [all f; (53.5, 39.5–71.0)], 31 (BN) [all f; (53.8, 26.6–85.4)], 36 (HC) [all f; (42.9, 20.1–78.1)]	SR (sFas/sFasL, sFas: ng/ml, sFasL: pg/ml), MPAA (Md, Rg): [total BRC (1.97/50.00, 1.05–11.78/50.00–164.31)], [HC (1.41/50.00, 0.78–3.25/50.00–178.82)] [DCIS (2.30/50.00, 1.38–4.19/50.00–55.09], [BN (2.01/50.00, 0.98–3.64/50.00–112.75)], sFas: [BRC: S-I (1.96, 1.05–3.79), S-II (1.95, 1.08–5.18), S-III (2.12, 1.21–5.48), S-IV (3.18, 1.50–11.78)]; $p < 0.0001$/p = 0.3418 (total BRC vs HC), p = 0.2357/p = 0.5207 (total BRC vs BN), p = 0.0006/p = 0.1518 (DCIS vs HC), $p < 0.0001$/p = 0.6995 (BN vs HC)	[64]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFasL, colorectal cancer (CRC)	Serum (SR) sFasL levels in patients with colorectal polyp (POL), but not those with CRC, were significantly higher than those in healthy controls (HC).	P: 20 (CRC) [11 m/9 f; (Md: 72, SD: 11, Rg: 49–81)], C: 20 (POL) [9 m/11 f; (68, 10, 56–80)], 20 (HC) [10 m/10 f; (62, 12, 55–77)]	SR (sFasL, pg/ml), MPAA (Md, Iqr): [CRC (nd, 14.49–26.55)], [POL (24.34, 20.84–42.36)], [HC (9.91, 6.445–17.63)]; $p < 0.001$ (POL vs HC)	[65]
DcR3, various cancers [breast cancer (BRC), gastric cancer (GAC), lymphoma (LYM), and others)	Serum (SR) DcR3 levels in patients with BRC, GAC, and LYM were significantly higher than those in healthy controls (HC). SR DcR3 levels could be used for the diagnosis of GAC and predicting cancer metastasis (ME) across multiple cancer types.	P: 90 [total cancers (TC), 58 [with metastasis (ME)] [25 m/33 f; (Mn: 51.5, SD: 12.2)], 32 (non-ME) [12 m/20 f; (47.4, 15.5)], 12 (BRC), 10 (GAC), 9 (LYM), 59 (other cancers), C: 25 (HC) [nd/nd; (nd, nd)]	SR (DcR3, pg/ml), ELISA (Mn, SD): [TC: ME (335.6, 413.6), non-ME (228.5, 173.7)], [TC: GAC (Md: ca. 320), LYM (ca. 280), BRC (ca. 250)], [HC (ca. 180)]; $p = 0.0061$ (GAC vs HC), $p = 0.023$ (BRC vs HC), $p = 0.041$ (LYM vs HC), $p < 0.05$ (ME vs non-ME)	[66]
sFasL, various cancers associated with pleural effusion (PE)	Pleural fluid (PF) sFasL levels were a negative predictor of malignant pleural effusion (MPE). Serum (SR) lactate dehydrogenase (LDH)/PF-sFasL ratio was identified as one of three parameters with the largest area under the curve (AUC) for differentiating between MPE and non-MPE. The highest diagnostic performance was found for SR-LDH × age/PF-sFasL.	P: 140 (total patients with PE) [76 m/64 f; (Md: 64.5, Iqr: 54–75)], 74 (MPE) [nd/nd; (Md: 69.0, Iqr: 60.0–77.0)], 37 [tuberculous PE (TPE)] [nd/nd; (52.0, 35.0–75.0)], 29 [parapneumonic PE (PPE)] [nd/nd; (59.0, 51.0–69.0)]	PF (sFasL, pg/ml), ELISA (not shown in measurement values); multivariate logistic regression analysis for MPE: $p = 0.04$, $\beta = -0.21$ (PF-sFasL), ROC curve analysis for differentiating between MPE and non-MPE: AUC = 0.802 (95% CI: 0.693–0.885) (PF-sFasL), AUC = 0.849 (95% CI: 0.747–0.922) (SR LDH/PF-sFasL), AUC = 0.866 (95% CI: 0.766–0.934) (SR LDH x age/PF-sFasL)	[67]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFasL, carcinogenesis caused by benzodiazepine (BD) treatment	Change in serum (SR) sFasL levels in overweight (OW), but not in normal-weight (NW), patients after BD treatment for six weeks reached statistical significance. Adiposity may have a potential for leading to lorazepam-associated carcinogenesis in OW patients.	P: 19 [total BD-treated patients (BD)] [all m; (Mn: 26.1, SD: 3.4)], 9 (OW) [all m; (26.1, 3.4)], 10 (NW) [all m; (25.3, 3.5)], measurement time-points: baseline (BE) and after treatment with 0.5 mg/day of BD for 6 weeks (6W)	SR (sFasL: pg/ml, BE/6W), MPAA (Mn, SD): [total BD (122.9/131.2, 20.4/23.7)], [BD: OW (120.4/137.0, 24.7/24.2), NW (125.1/125.9, 16.8/23.1)]; p = 0.034 (total BD: BE vs 6W), p = 0.005 (BD-OW: BE vs 6W), p = 0.856 (BD-NW: BE vs 6W)	[68]
sFasL, breast cancer (BRC) (infiltrating ductal carcinoma)	Serum (SR) sFasL levels were significantly higher in patients with BRC compared to age-matched non-BRC controls, at presentation, post-surgery, and post-chemotherapy. The greatest difference in SR sFasL levels was observed between patients with 1-3 malignant lymph nodes (N1-3) and those with 0 nodes (N0) at any measurement time-point. SR sFasL levels had prognostic potential in patients with BRC.	P: 24 (total BRC) [all f; (Mn: 44.75, Rg: 25–75), [number of malignant lymph-nodes (N): N0, N1-3, N > 3], measurement time-points: at presentation (PRE), at post-surgery (POS), at post-chemotherapy (POC)], C: nd (non-BRC) [all f; (age-matched)]	SR (sFasL: PRE/POS/POC, nd), ELISA (Md, Iqr): [total BRC (73.0/58.0/64.85, 35.76–90.00/40.0–85.0/26.75–89.50)], [non-BRC (22.5, 12.5–37.5)], [BRC: N0 (34.3/40.0/42.0, 15.6–75.3/20.57–40.0/13.4–60.8), N1-3 (86.0/79.6/84.1, 61.0–95.0/55.5–129.5/47.0–101.2), N > 3 (40.0/42.0/35.0, 11.5–76.6/19.9–65.0/24.6–79.0)]; p = 0.004/p = 0.001/p = 0.010 (total BRC vs non-BRC), p = 0.001/p = 0.001/p = 0.001 (N0 vs N1-3)	[69]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas and sFasL, cervical cancer (CEC) (invasive)	Cervicovaginal lavages (CVL) sFas and sFasL levels in patients with invasive CEC (ICEC) were significantly higher than those with non-ICEC with intraepithelial lesions (IL) and healthy controls (HC). Elevation of CVL sFasL levels was negatively correlated with *Lactobacillu*s abundance (LA) and positively correlated with vaginal pH (VPH) and inflammation scores (IS). CVL sFas and sFasL levels were good indices for discriminating ICEC from related non-ICEC cervical diseases.	P: 10 (ICEC) [all f; (Mn: 38.90, SD: 9.09)], 27 [high-grade IL (IL-H)] [all f; (38.2, 8.46)], 12 [low-grade IL (IL-L)] [all f; (35.08, 7.24)], C: 11 [HC-human papillomavirus (HPV) positive (HC-HPV)] [all f; (36.36, 9.53)], 18 [HC-HPV negative (HC-non-HPV)] [all f; (40.38, 6.98)]	CVL (sFas/sFasL, pg/ml), MPAA (Md): [ICEC (ca. 280/ca. 3.0)], [IL: H (ca. 60/ca. 0.63), L (ca. 100/ca. 1.1)], [HC: HPV (ca. 70/ca. 1.0), non-HPV (ca. 110/ca. 0.70]; $p < 0.0001$/$p < 0.0001$ (ICEC vs IL-H), $p < 0.001$/$p < 0.01$ (ICEC vs IL-L), $p < 0.0001$/$p < 0.05$ (ICEC vs HC-HPV), $p < 0.01$/$p < 0.001$ (ICEC vs HC-non-HPV), Corr. (vs sFasL): $p < 0.05$, $r = -0.27$ (LA), $p < 0.01$, $r = 0.33$ (VPH), $p < 0.01$, $r = 0.34$ (IS), ROC curve analysis for cancer detection (sFasL): $p < 0.0001$, AUC = 0.87	[70]
DcR3, pancreatic cancer (PAC)	Serum (SR) DcR3 levels in PAC patients were significantly higher than those in healthy controls (HC). SR DcR3 levels had a significant positive correlation with DcR3 expression levels in tumor tissues (TT-DcR3). The difference in TT-DcR3 levels affected some clinicopathological features, including tumor size (TS), lymph node metastasis (LNM), and clinical stage (CS). Positive TT-DcR3 levels were associated with shorter overall survival of patients with PAC.	P: 112 (total PAC), [AJCC staging system: 28 stage I (SI), 36 SII, 26 SIII, 22 SIV)], 64 (SI and SII) [31 m/33 f; (25 ≤ age 65, 39 > age 65)], C: 40 (HC) [nd/nd; (nd)]	SR (DcR3, pg/ml), ELISA (Md, Iqr): [total PAC (ca. 75, ca. 45–ca. 87)], [HC (ca. 30, ca. 23–ca. 35)]; $p < 0.001$ (total PAC vs HC), Corr. (vs SR DcR3): $p = 0.0023$, $r = 0.37347$ (TT-DcR3), TT-DcR3 (positive vs negative): $p = 0.040$ (larger TS), $p = 0.037$ (LNM presence), $p = 0.010$ (advanced CS), log-rank test for overall survival: $p = 0.098$ (TT-DcR3: positive vs negative)	[71]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFas and sFasL, colorectal cancer (CRC) (adenocarcinoma)	A significant overall difference in serum (SR) sFas, but not sFasL, levels among all CRC groups and healthy controls (HC) was identified using the Kruskal-Wallis test (KW). However, no significant difference between individual groups was found for both SR sFas and sFasL levels.	P: 216 (total CRC), 16 [highly differentiated (HD)] [6 m/10 f; (Md: 65, Iqr: 58–68.5)], 175 [moderately differentiated (MD)] [95 m/80 f; (67, 60.5–73)], 25 [low differentiated (LD)] [11 m/14 f; (65, 59–68)], C: 97 (HC) [34 m/63 f; (58, 45–67)]	SR (sFas/sFasL, pg/ml), MPAA (Md, Iqr): [CRC: HD (1672.4/46.58, 1453.9–3165.4 /16.1–67.51, MD (2037.1/54.54, 1547.2–2857.2/29.29–76.16), LD (1483.3/54.54, 1394.1–1696.4/39.39–61.81)], [HC (1870.5 /42.14, 1355.7–2427.4/25.4–59.78)]; p (KW) = 0.015/p = 0.23 (among CRC: HD, MD, LD, HC)	[72]
sFasL, pancreatic neuroendocrine neoplasms (PNEN)	Serum (SR)/plasma (PL) sFasL levels in patients with PNEN grade 3 (PNEN-G3) were significantly lower than those in healthy controls (HC). SR sFasL levels in patients with PNEN-G3 were negatively correlated to the expression level of the cell-growth fraction marker Ki-67 antigen index.	P: 42 (total PNEN-G3) [27m/15 f; (Md: 59, Rg: 27–80)], Ki-67 antigen expression index (Ki-67E): 30 (< 55%), 12 (> 55%), C: 42 (HC) (gender- and age-matched)	SR or PL (sFasL, arbitrary unit), MPAA (PEA) (Md, Iqr): [total PNEN-G3 (ca. 5.1, ca. 4.7–ca. 5.6)], [HC (ca. 5.6, ca. 5.3–ca. 6.1)]; $p < 0.05$ (PNEN-G3 vs HC), linear regression analysis (vs sFasL in PNEN-G3, unadjusted): $p < 0.05$ (Ki-67E)	[73]
sFas and sFasL, head and neck cancer (HNC)	Plasma (PL) sFasL levels in patients with HNC were significantly lower than those in healthy controls (HC), however, PL sFas levels demonstrated the opposite trend. An index composed of the PL sFasL level multiplied by PL gelsolin level (pGSN-sFasL) could be a novel biomarker for early detection of HNC.	P: 202 (total HNC) [nd/nd; (Md: 53, Rg: 22–81)], tumor stage: 33 stage I (S-I), 52 (S-II), 40 (S-III), 77 (S-IV), C: 45 (HC) [nd/nd; (nd, nd)]	PL (sFas/sFasL, pg/ml), MPAA (Mn, SEM): [total HNC (1538/29.3, 54.36/3.596)], [HC (1111/66.89, 57.76/12.87); $p < 0.001$/$p < 0.001$ (total HNC vs HC), ROC curve analysis for early detection of HNC: $p < 0.001$, AUC = 0.877 (sFasL), $p < 0.001$, AUC = 0.950 (pGSN-sFasL)	[74]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFasL, biliary tract cancer (BTC) (unresectable or metastatic)	Serum (SR) sFasL levels in total and responding patients with BTC (RP) after two cycles of nivolumab (NIV) treatment combined with gemcitabine (GEM) and cisplatin (CPT) were significantly lower than their baseline levels. A decrease (Δ) in SR sFasL levels was significantly larger in RP compared to non-responders (non-RP) and in patients with longer overall survival. A large decrease in SR sFasL levels could predict better outcome of immune checkpoint inhibitor-based combination therapy.	P: 32 (total enrolled BTC) [18 m/14 f; (Md: 60, Rg: 27–69)], 27 (total finally analyzed BTC), 6 [resistant to GEM-based or CPT-based chemotherapy (RES)], 21 [chemotherapy-naïve (NAI)], measurement time-points: baseline (BS) and after 2 cycles of NIV treatment combined with GEM and CPT (AF)	SR (sFasL: BS/AF, pg/ml), MPAA (Mn, SD): [total BTC (ca. 3.0/ca. 2.0, ca. 3.4/ca. 1.6)], [BTC: RP (ca. 3.1/ca. 1.3, ca. 3.4/ca. 0.57), non-RP (ca. 2.5/ca. 2.5, ca. 4.2/ca. 2.1)]; $p \leq 0.05$ (total BTC: BS vs AF), $p \leq 0.01$ (BTC-RP: BS vs AF), $p = 0.012$ [Δ (BTC-RP: BS vs AF) vs Δ (BTC-non-RP: BS vs AF)], log-rank test for overall survival (sFasL: decreased vs increased): $p = 0.00076$, HR = 5.766	[75]
sFasL, renal cell cancer (RCC) (metastatic)	Serum (SR) sFasL levels in patients with metastatic RCC (mRCC) were not significantly different between before treatment and after four weeks treatment with axitinib (AXT). Change in SR sFasL levels caused by AXT treatment did not show significant association with either shorter progression-free survival (PFS) or shorter overall survival (OS).	P: 44 (mRCC) [31 m/13 f; (Md: 66.5, Rg: 24–83)], measurement time-points: pre-treatment (PRE) and 4 weeks after initiation of AXT treatment (4W)	SR (sFasL, pg/ml), MPAA (Md, Rg): [mRCC: PRE (298, 259–396), 4W (278, 226–420)]; $p = 0.118$ (mRCC: PRE vs 4W), risk analysis for survival (sFasL: increased vs decreased): $p = 0.347$, HR = 1.457 (95% CI: 0.665–3.193) (shorter PFS), $p = 0.693$, HR = 1.228 (95% CI: 0.443–3.399) (shorter OS)	[76]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices from various statistical analyses	Refs.
sFasL, head and neck cancer (HNC)	Serum (SR) sFasL levels in patients with HNC co-treated with 40 or 80 mg/ml pantoprazole (PAN-40/PAN-80) to avoid nephrotoxicity were significantly lower than those in patients without PAN co-treatment (non-PAN), after one and three cycles of cisplatin treatment (CPT). A change in SR sFasL levels after CPT with/without PAN showed a similar trend to those in urinary levels of some acute kidney injury markers corrected to SR creatinine.	P: 60 (total HNC with CPT), 20 (PAN-80) [14 m/6 f; (Mn: 52.80, SD: 13.25)], 20 (PAN-40) [15 m/5 f; (59.65, 12.59)], 20 (non-PAN) [12 m/8 f; (51.45, 14.76)], measurement time-points: before (BS), after 48h of 1st (AF1) and 3rd cycles (AF3) of CPT administration	SR (sFasL, ng/ml), ELISA (Mn, SD): [HNC-PAN-80: BS (7.26, 1.69), AF1 (9.11, 2.59), AF3 (10.87, 2.86)], [HNC-PAN-40: BS (7.26, 1.69), AF1 (9.98, 2.95), AF3 (11.70, 2.54)], [HNC-non-PAN: BS (7.93, 1.73), AF1 (14.20, 4.84), AF3 (17.63, 5.46)]; $p < 0.05$ (HNC-AF1/AF3: PAN-40/80 vs non-PAN), $p < 0.001$ (HNC-AF1/AF3: among non-PAN, PAN-40, PAN-80)	[77]
sFas, breast cancer (BRC) (ductal, medullary, lobular, and hormone-dependent carcinoma)	Saliva (SAL) sFas, but not sFasL, levels in patients with BRC were significantly higher than those in non-BRC controls. However, changes in SAL sFas levels according to the difference in TNM stages showed no statistical significance. SAL sFas levels discriminated BRC patients from healthy controls and appeared to be a promising tool for BRC diagnosis with similar efficacy to cancer antigen-125 (CA-125).	P: 91 (total BRC) [all f; (Mn: 51.6, SD: 10.4)], tumor stage (TNM): 29 stage IA (S-IA), 21 (SII-A), 6 (S-IIB), 29 (S-IIIA), 2 (S-IIIC), 4 (S-IV), C: 60 (non-BRC) [all f; (55.7, 14.2)]	SAL (sFas/sFasL, pg/ml), MPAA (Md, Rg): [total BRC (145.9/2.9, 35.4–1524.0/1.3–16.0)], [non-BRC (84.1/2.6, 4.9–349.1/41.0–14.3)], sFas: [BRC: S-IA (1305.2, 399.94–444.48), S-IIA & IIB (1723.5, 83.74–1524.00), S-IIIA & IIIC & S-IV (1441.2, 35.37-473.98); $p = 0.008/0.233$ (total BRC vs non-BRC), $p = 0.508$ (sFas) (BRC: among S-IA, S-IIA & IIB, S-IIIA & IIIC & S-IV), ROC curve analysis for BRC diagnosis: AUC = 0.67 (sFas), AUC = 0.68 (CA-125)	[78]

3.2. Autoimmune and allergic diseases [79–114]

To date, SLE has been the most extensively investigated target disease for the possible use of sFas and sFasL among various autoimmune diseases (Table 2). The SR/PL levels of sFas and sFasL in patients with SLE were significantly elevated compared to those in healthy controls [79,84,87,94,96,107,110]. SR sFas levels are closely related to disease severity in patients with SLE. The clinical parameters or disease symptoms that showed remarkable differences in SR sFas levels between the patients in active and severe phases and those in inactive phases included SLE disease activity index [79,84,87], lupus nephritis (LN) [94], flare (FL) [96,110], coronary artery disease (CAD), and carotid plaques [107]. SR sFas levels were promoted as a possible biomarker of genetic susceptibility to LN in patients with SLE [94]. PL sFasL levels were identified as a marker exhibiting a prominent increase in the FL period as compared to those in the non-FL period of the same SLE patients [96], while the sFasL level showed a significant association with FL occurrence over time [110].

To date, SR/PL sFasL levels alone have been the most intensively examined for possible clinical use in patients with ALPS [86,92,93,97,108]. sFasL levels were predominantly higher in patients with definite ALPS possessing a homozygous or heterozygous mutation in either the germline or somatic Fas receptor gene than in patients with ALPS-like diseases lacking causative mutations [86] or unknown gene mutations [108], non-ALPS or healthy relatives with Fas gene mutation [92], and healthy mutation-positive relative controls [97]. Thus, the SR sFasL level could be an efficient biomarker for presumptive diagnosis before molecular diagnosis in patients with possible ALPS [92,97]. A significant drop in PL sFasL levels was observed in all patients with ALPS possessing heterozygous Fas gene mutations after treatment with low-molecular-weight immunosuppressive agents [86].

Mean SR sFas levels in patients with rheumatoid arthritis (RA) were higher than those in healthy controls but lower than those in SLE patients [79]. Synovial fluid (SF) DcR3 levels were significantly higher than SR DcR3 levels in the same patients [100]. Several studies on the body fluid levels of sFas, sFasL, and DcR3 in patients with RA have evaluated the effects of drug treatments and disease activity [88,98,100]. Both SR sFas and sFasL levels in patients with RA treated with the IL-1 inhibitor anakinra, but not with the corticosteroid prednisolone, or a placebo drug, significantly decreased in association with improvements in impaired left ventricular performance in patients with RA [88]. In contrast, the SR sFas levels, but not the SR sFasL levels, in RA patients significantly increased after treatment with an anti-tumor necrosis factor (TNF)-α antibody-based drug, adalimumab or infliximab, and the recovered patients with clinical remission (CR) had significantly elevated SR sFas levels compared to patients who did not achieve CR [98]. SF/SR DcR3 levels in patients with RA were significantly higher than those with osteoarthritis and healthy controls [95,100]. SF DcR3 levels exhibited a marked negative correlation with disease activity indices, presenting deteriorated joint functions in patients with RA [95], and low levels of SR DcR3 were associated with the progression of atheromatous lesions [89]. SR DcR3 levels in patients with RA significantly decreased after treatment with anti-TNF-α drugs, whereas DcR3 levels were not significantly affected by the status of some clinical features in RA, including the levels of rheumatoid factor and anti-cyclic citrullinated peptide antibody [100].

Table 2. Possible usage of sFas, sFasL, and DcR3 as clinical biomarkers in autoimmune and allergic diseases.

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), Sjögren's syndrome (SS)	Serum (SR) sFas levels in patients with SLE were significantly higher than the levels in those with other autoimmune diseases and healthy controls (HC). SR sFas levels in patients with active SLE were significantly higher than those with inactive SLE. SR sFas levels in patients with SLE were significantly correlated with various important laboratory clinical parameters, including SLE disease activity index (SLEDAI) score, anti-DNA antibody (ADA) level, and leucocyte counts (LC). SR sFas levels can serve as an indicator for SLE disease activity.	P: 203 (total autoimmune diseases), 77 (total SLE) [10 m/67 f; (nd)], 28 [SLEDAI ≥ 10 (ACT)), 49 [SLEDAI ≤ 9 (INACT)], 60 (RA) [11 m/49 f; (nd)], 19 (SSc) [all f; (nd)], 13 (PM/DM) [3 m/10 f; (nd)], 34 (SS) [all f; (nd)], C: 40 (HC) [22 m/18 f; (nd)]	SR (sFas, ng/ml), ELISA (Mn, SD): [total SLE (0.87, 1.54)], [RA (0.38, 0.81)], [SSc (0.24, 0.27)], [DM/PM (0.30, 0.24)], [SS (0.31, 0.37)], [HC (0.22, 0.25)], [SLE: ACT (1.58, 2.36), INACT (0.46, 0.40)]; $p < 0.001$ (total SLE vs HC, RA), $p = 0.006$ (total SLE vs SSc), $p = 0.004$ (total SLE vs SS), $p = 0.011$ (SLE: ACT vs INACT), Corr. (sFas in total SLE): $p = 0.037$, $r_s = 0.240$ (SLEDAI), $p < 0.001$, $r_s = 0.292$ (ADA), $p = 0.006$, $r_s = -0.342$ (LC)	[79]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas, Graves' ophthalmopathy (GO)	Serum (SR) sFas levels in patients with sub-group GO lacking diplopia (DIP) or extraocular muscle hypertrophy (EMH) symptoms, but not in total GO patients, were significantly lower than those in healthy controls (HC). SR sFas levels in patients with GO with DIP or EMH, but not in those with proptosis, were significantly higher than those with GO lacking each corresponding symptom.	P: 43 (total GO) [10 m/33 f; (Mn: 43, Rg: 15–74)], 24 [with DIP (DIP)], 19 (non-DIP); 27 [with EMH (EMH)], 16 (non-EMH); 24 [with proptosis (PRO)], 19 (non-PRO)], C: 11 (HC) [2 m/9 f; (36, 23–51)]	SR (sFas, ng/ml), ELISA (Mn, SD): [total GO (1.35, 2.03)], [HC (0.93, 0.32)], [GO: DIP (1.98, 2.56), non-DIP (0.56, 0.24); EMH (1.81, 2.46), non-EMH (0.58, 0.26); PRO (1.15, 0.98), non-PRO (1.61, 2.88)]; $p < 0.001$ (GO: non-DIP, non-EMH vs HC); $p < 0.01$ (GO: DIP vs non-DIP; GO: EMH vs non-EMH), p = ns (total GO vs HC; GO: PRO vs non-PRO)	[80]
sFas and sFasL, Graves' hyperthyroidism (GH)	Serum (SR) sFas and sFasL levels of untreated patients with GH with high levels of thyroid-stimulating hormone (TSH) receptor antibodies (TRAb) were significantly higher than those drug-treated with low TRAb levels and healthy control (HC). sFasL levels in patients with GH changed along a wide range with TRAb levels, including the region of the low level. SR sFasL levels may be used as a marker for evaluating disease aggression or regression in GH.	P: 44 (total GH), 22 [high TRAb with ≥ 50% inhibition of TSH binding (H-TRAb)] [6 m/16 f; (Mn: 37.2, SD: 10.9, Rg: 20–45)], 22 [low TRAb (≤ 20 % inhibition of TSH binding) (L-TRAb)] [1 m/21 f; (42.9, 14.3, 26–65)], C: 22 (HC) [8 m/14 f; (33.8, 8.9, 22–45)]	SR (sFas/sFasL, ng/ml), ELISA (Mn, SD): [GH: H-TRAb (1.56/0.153, 0.26/0.018), L-TRAb (0.76/0.126, 0.26/0.112)], [HC (0.79/0.076, 0.24/0.010)]; $p < 0.01$/$p < 0.01$ (GH-H-TRAb vs GH-L-TRAb, HC), p = ns/$p < 0.01$ (GH-L-TRAb vs HC), Corr.: $p < 0.01$, $r = 0.91$ (sFas vs TRAb), $p < 0.01$, $r = 0.69$ (sFasL vs TRAb), $p < 0.01$, $r = 0.71$ (sFas vs sFasL)	[81]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas, autoimmune hepatitis type 1 (A1H) and chronic hepatitis C with autoimmune features (C-A1H)	Serum (SR) sFas levels in patients with C-A1H were significantly higher than those in chronic hepatitis patients without autoimmune features (C-CH) and healthy controls (HC). SR sFas levels in patients with C-CH, but not those with C-A1H, showed significant positive correlations with alanine aminotransferases (ALT) and aspartate aminotransferases (AST).	P: 10 (A1H) [all f; (Md: 56, Rg: 42–71], 18 (C-A1H) [6 m/12 f; (56, 55–65/49–69)], C: 34 (C-CH) [19 m/15 f; (53, 31–67/42–71)], 16 [systemic lupus erythematosus (SLE)] (nd/nd; nd), 23 (HC) [16 m/7 f; (45, 27–62/27–67)]	SR (sFas, ng/ml), ELISA; P (Mn, SD, Rg): [A1H (710, 133, 576-843)], [C-A1H (752, 288, 465–1040)], [C-CH (514, 260, 255–774)], [SLE (555, 286, 270–841)], [HC (495, 176, 320–671)]; $p < 0.05$ (C-A1H vs C-CH, HC), Corr. (vs sFas in C-AIH/in C-CH): $p = 0.934$/$p = 0.006$, $r = 0.021$/$r = 0.461$ (AST), $p = 0.520$/$p = 0.004$, $r = 0.164$/$r = 0.473$ (ALT)	[82]
sFas, familial Mediterranean fever (FMF) complicated with/without amyloidosis (AMY)	Serum (SR) sFas levels in patients with FMF with amyloidosis (FMF-AMY) were significantly lower than those without AMY (FMF-non-AMY) and healthy controls (HC). SR sFas levels in patients with FMF showed a significant negative correlation with disease duration (DD).	P: 10 [FMF with AMY (FMF-AMY)] [5 m/5 f; (Md: 41.5, Rg: 33–51)], 12 (FMF-non-AMY) [7 m/ 5 f; (23.5, 17–38)], C: 14 (HC) [6 m/8 f; (46, 38–57)]	SR (sFas, pg/ml), ELISA; P (Md, Rg): [FMF: AMY (1338, 453–3240), non-AMY (4630, 2580–12270)], [HC (3430, 2110–5960)]; $p < 0.05$ (FMF-AMY vs FMF-non-AMY, HC; FMF-non-AMY vs HC), Corr. (vs sFas): $p < 0.01$, $r = -0.729$ (DD)	[83]
sFas, systemic lupus erythematosus (SLE)	Serum (SR) sFas levels in patients possessing active lupus with SLE disease activity index (SLEDAI) ≥ 20 were significantly higher than those in patients with inactive lupus (SLEDAI ≤ 8) and healthy controls (HC).	P: 25 (total SLE) [nd/nd; (nd)], 14 [SLEDAI ≥ 20 (ACT)], 11 [SLEDAI ≤ 8 (INACT)], C: 18 (HC) [nd/nd, (nd)]	SR (sFas, ng/ml), ELISA (Mn, SD): [SLE: ACT (ca. 2.1, ca. 0.5), INACT (ca. 0.35, ca. 0.25)], [HC (ca. 0.1, ca. 0.15)]; $p < 0.01$ (SLE-ACT vs SLE-INACT, HC)	[84]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas, silicosis (SIL) with alterations in autoimmunity	Serum (SR) sFas levels in patients with SIL were not significantly different from those in healthy controls (HC). However, SR sFas levels in some patients with SIL exceeded normal range.	P: 10 (SIL) [7 m/3 f; (Mn: 74.4, SD: 8.7)], C: 10 (HC) [6 m/4 f; (60.6, 5.8)]	SR (sFas, ng/ml), ELISA (Mn, SD): [SIL (1.93, 0.29)], [HC (Rg: ≤ 2.2)]	[85]
sFasL, autoimmune lymphoproliferative syndrome (ALPS)	Plasma (PL) sFasL levels in patients with ALPS with Fas receptor gene-mutation (*FAS*-m) were significantly higher than the levels in those with non-ALPS with *FAS*-m (MPR), ALPS-like without causative mutations (ALPS-like), healthy relatives (HR), and healthy controls (HC). A significant drop in PL sFasL levels was observed in all patients with ALPS with heterozygous *FAS*-m during immunosuppressive treatment (IST). PL sFas levels effectively diagnosed ALPS.	P: 54 (total ALPS), [nd/nd, (nd)], 3 [with homozygous *FAS*-m (ALPS-0)], 41 [with germinal heterozygous *FAS*-m (ALPS-Ia)], 10 [with somatic heterozygous *FAS*-m (ALPS-Im)], C: 12 (ALPS-like), 24 (MPR), 41 HR without *FAS*-m (HR), 21 (HC) (gender-matched), measurement time-points (ALPS-Ia/Im, n = 8): before (BE) and during (DU) IST	PL (sFasL, ng/ml), ELISA (Mn): [ALPS: ALPS-0 (ca. 91), ALPS-Ia (ca. 2.5), ALPS-Im (ca. 2.7), ALPS-like (ca. 0.2)], [MPR (ca. 0.3)], [HR (ca. 0.1)], [HC (ca. 0.1)]; $p < 0.0001$ (ALPS-1a vs MPR, HC), $p = 0.0003$ (MPR vs HC), $p = 0.0014$ (ALPS-like vs HC), $p = 0.0102$ (ALPS-0 vs ALPS-1a), p = ns (ALPS-Ia vs ALPS-Im), $p = 0.0078$ (ALPS-Ia/Im-IST: BE vs DU)	[86]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas, systemic lupus erythematosus (SLE)	Serum (SR) sFas levels in patients with SLE were significantly higher than those in healthy controls (HC). SR sFas levels in patients with SLE significantly increased in active phases compared to those of inactive phases. SR sFas levels significantly correlated with the SLE disease activity index (SLEDAI).	P: 114 (total SLE) [9 m/105 f; (Mn: 30.7, SD: 9.55, Rg: 13–62)], 56 [SLEDAI ≥ 10 (ACT)], 58 [SLEDAI < 9 (INACT)], C: 50 (HC) [4 m/45 f; (29.5, 7.21, 20–50)]	SR (sFas, pg/ml), ELISA (Mn, 2SD): [total SLE (372.20, 228.35)], [HC (190.38, 127.77)], [SLE: ACT (493.88, 525.27), INACT (254.82, 182.61)]; p = 0.001 (total SLE vs HC, SLE: ACT vs INACT), Corr. (vs sFas): p = 0.001, r = 0.494 (SLEDAI)	[87]
sFas and sFasL, rheumatoid arthritis (RA)	Serum (SR) sFas and sFasL levels in patient with RA treated with the interleukin-1 inhibitor anakinra (ANA), but not the corticosteroid prednisolone (PRE), significantly decreased. Impaired left ventricular (LV) deformation indices, including the ratio of mitral E wave measured by pulsed-wave Doppler to early diastolic velocity (E/Em) and average longitudinal peak systolic strain rate (LongSRS), in patients with RA were improved after ANA treatment. These changes (Δ) were significantly correlated with Δ SR sFas levels in patients with RA.	P: 46 (total RA) [15 m/31 f; (Mn: 56, Rg: 16)], 23 [treated with ANA (ANA)] [6 m/17 f; (57, 17)], 23 [treated with PRE (PRE)] [7 m/16 f; (56, 16)], 11 [treated with placebo (PLA)] [nd/nd; (nd, nd)], measurement time-points: baseline (BS), after 30 days (30D) and/or 3h (3H) treatment with drugs.	SR (sFas/sFasL, pg/ml), ELISA (Mn, Iqr): [BS: ANA (481/289, 267–567/187–437), PRE (476/282, 238–586/197–421), PLA (485/285, 273–570/188–442)], [3H: ANA (364/221, 249–393/141–278)], [30D: ANA (301/190); PRE (487/291)]; p = 0.004/p = 0.001 (ANA: BS vs 3H), p = 0.003/p < 0.001 (ANA: BS vs 30D), p = 0.374/p = 0.386 (PRE: BS vs 30D), Corr. (vs ΔsFas in ANA): p = 0.03, r = −0.52 (ΔE/Em), p = 0.04, r = 0.49 (ΔLongSRS)	[88]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
DcR3, rheumatoid arthritis (RA) (non-diabetic)	Low serum (SR) DcR3 and TL1A levels in non-diabetic RA patients were associated with a significantly low probability of new plaque formation in either carotid arteries (CA) alone or that in CA and/or common femoral arteries (FA) during the 3.5-year follow-up period.	P: 45 (total RA) [7 m/38 f; (Mn: 59.0, SD: 13.4)], 16 [with undetectable DcR3 in combination with TLIA levels lower than the arbitrary cut off value (1.75 ng/ml)] (LDT), 29 [all others (non-LDT)]	SR (DcR3, pg/ml), ELISA (Md, Iqr): [RA: LDT (0.0, 0.0-0.0), non-LDT (0.0, 0.0–6.8)]; p = 0.032 (LDT vs non-LDT), risk analysis for new CA/FA formation during next 3.5 year (LDT vs non-LDT): p = 0.026, OR = 0.153 (95% CI: 0.029–0.798) (CA), p = 0.022, OR = 0.204 (95% CI: 0.052–0.792) (CA and/or FA)	[89]
sFas and sFasL, multiple sclerosis (MS)	Serum (SR) sFas and sFasL levels in patients with MS were not significantly different from those in healthy controls (HC). SR sFas and sFasL levels could not discriminate HC from total MS patients or various clinical forms of MS patients. SR sFas and sFas levels failed to discriminate patients in relapsing-remitting MS (RRMS) in clinical remission (CR) from RRMS patients during relapse (DR).	P: 67 (total MS) [31 m/36 f; (Mn: 42.5, SD: 10.7)], 30 [primary progressive (PPMS)] [16 m/14 f; (50.2, 8.6)], 37 [relapsing-remitting (RRMS)] [15 m/22 f; (36.3, 7.8)], C: 36 (HC) [8 m/28 f; (34.7, 9.5)]	SR (sFas/sFasL, pg/ml), MPAA (Md, Iqr): [RRMS: CR (ca. 810/ca. 17, ca. 650–ca. 1200/ca. 7.4–ca. 24), DR (ca. 840/ca. 14, ca. 550–ca. 1000/ca. 8.1–ca. 18)], differences in Mn from HC: [total MS (−105.0/0.2), RRMS (−80.4/0.7), PPMS (−184.7/−1.4)]; p = 0.501/p = 0.949 (total MS vs HC), p = 0.624/p = 0.841 (RRMS vs HC), p = 0.407/p = 0.761 (PPMS vs HC), p = 0.474/p = 0.708 (RRMS: CR vs DR)	[90]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, collagen diseases (CD)	Neither serum (SR) sFas nor SR sFasL levels discriminated acute-onset diffuse interstitial lung disease (AoDILD) state from stable disease (ST) state in patients with CD.	P: 25 (CD) [11 m/14 f; (Mn: 65.9, SD: 10.8)], measurement time-points: AoDILD state and ST state	SR (sFas/sFasL, pg/ml), MPAA (Mn, SD): [CD: AoDILD (3450/74, 13337/74), ST (2237/68, 9967/63)]; p = 0.715/0.763 (CD: AoDILD vs ST)	[91]
sFasL, autoimmune lymphoproliferative syndrome (ALPS)	Serum (SR) sFasL levels in patients with ALPS with Fas receptor gene mutation (*FAS*-m) of germline (ALPS-FAS) or somatic *FAS*-m (ALPS-sFAS) were significantly higher than those in patients without *FAS*-m. Initial SR sFasL and vitamin B_{12} (VB_{12}) levels assessment combined with *FAS* gene sequencing was the most efficient and cost-effective approach for the molecular diagnosis of ALPS.	P: 163 (total ALPS) [nd/nd (nd)], 38 (total ALPS with *FAS*-m), 32 (ALPS-FAS), 6 (ALPS-sFAS), C: 9 (defective Fas-mediated apoptosis *in vitro* without mutation in *FAS*, *FASL* or *CASP-10*) (ALPS-U), 116 (total normal or unknown Fas-mediated apoptosis *in vitro*), 51 [no mutation in *FAS*, *FASL* or *CASP-10* genes (ALPS-ph-sq)], 65 [*FAS* was not sequenced (ALPS-ph-nsq)]	SR (sFasL, pg/ml), ELISA(Md): [ALPS-FAS (ca. 1400), ALPS-sFAS (ca. 1900)], [ALPS-U (ca. 290), ALPS-ph-sq (ca. 160), ALPS-ph-nsq (ca. 120)]; p < 0.001 (among ALPS-FAS, ALPS-sFAS, ALPS-U, ALPS-ph-sq, LPS-ph-nsq), ROC curve analysis for diagnosis of *FAS*-m: AUC = 0.91 (95% CI: 0.83–0.98) (sFasL), predictive value for *FAS*-m (positive/negative, using cut-off values: sFasL: 559 pg/ml, VB12: 1255 pg/ml): 92%/97% (sFasL combined with VB12)	[92]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFasL, common variable immunodeficiency (CVID) and autoimmune lymphoproliferative syndrome (ALPS)	Serum (SR) sFasL levels were not significantly different between patients with common variable immunodeficiency (CVID) and healthy controls (HC). SR sFasL levels can be used to discriminate patients with CVID from ALPS with germline *FAS* gene mutations (ALPS-FAS), despite their overlapping clinical phenotypes.	P: 13 (CVID) [6 m/7 f; (Md: 50, Rg: 23–71)], 2 (ALPS-FAS) [nd/nd; (nd, nd), C: 33 (HC) [14 m/19 f; (34, 21–68)]	SR (sFasL, pg/ml), ELISA (Mn, number of >200 pg/ml patients: measured values): [CVID (ca. 100, 1: ca. 220)], [ALPS-FAS (nd, 2: ca. 1300, ca. 1600)], [HC (ca. 95, 0)]; p: ns (CVID vs HC)	[93]
sFas, systemic lupus erythematosus (SLE) with/without lupus nephritis (LN)	Serum (SR) sFas levels in patients with systemic lupus erythematosus (SLE) with lupus nephritis (LN) exhibiting protein-urea were significantly higher than the levels in those with SLE without LN and healthy controls (HC). SR sFas levels were significantly elevated in patients with LN with G/G genotypes and those with non-LN SLE with A/G. SR sFas levels may be used as an alternate biomarker for genetic susceptibility in patients with SLE regarding LN.	P: 67 (total SLE) [14 m/53 f; (Mn: 41.2, SD: 22.1)], 24 [with LN (LN)], 43 (non-LN), C: 54 (HC) [8 m/46 f; (34.3, 14.51)], −670 A/G Fas receptor gene (*FAS*) polymorphism (A/A, A/G, G/G) was identified with the samples in each group.	SR (sFas, pg/ml), ELISA (Mn, SD): [total SLE: LN (1342.997, 337.10), non-LN (845.84, 444.66)], [total HC (630.44, 385.34)], [SLE-LN: A/A (ca. 840), A/G (ca. 1240), G/G (ca. 1470)], [SLE-non-LN: A/A (ca. 770), A/G (ca. 1350), G/G (ca. 720)], [HC: A/A (ca. 500), A/G (ca. 640), G/G (ca. 640)]; $p = 0.01$ (SLE: total LN vs total non-LN), $p < 0.001$ (total SLE-LN vs total HC), $p < 0.05$ (G/G: SLE-LN vs SLE-non-LN, HC; SLE-non-LN: A/G vs A/A, G/G)	[94]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
DcR3, rheumatoid arthritis (RA)	Synovial fluid (SF) DcR3 levels in patients with rheumatoid arthritis (RA) were significantly higher than the levels in those with osteoarthritis (OA). SF DcR3 levels in patients with RA were significantly correlated with clinical indices, including erythrocyte sedimentation rate (ESR), tender/swollen joint count (T-JC/S- JC), general health (GH), and disease activity score using 28 joint counts (DAS28 score). SF DcR3 levels may be used as a biomarker for RA disease-activity evaluation.	P: 32 (RA) [5 m/27 f; (Mn: 50.7, SEM: 2.9)], C: 12 (OA) [4 m/8 f; (62.0, 3.5)]	SF (DcR3, pg/ml), ELISA (Mn, SD) [RA (3237.6, 1623.2)], [OA (1594.8, 1190.0)]; $p = 0.003$ (RA vs OA), Corr. (vs DcR3): $p = 0.002$, $r = -0.560$ (ESR), $p = 0.003$ $r = -0.498$ (T-JC), $p = 0.003$, $r = -0.487$ (S-JC), $p = 0.001$, $r = -0.527$ (GH), $p < 0.001$, $r = -0.579$ (DAS28 score)	[95]
sFas and sFasL, systemic lupus erythematosus (SLE) with/without flare (FL)	Baseline plasma (PL) sFas and sFasL levels were significantly higher in patients with SLE with subsequent FL than the levels in those with non-FL. PL sFasL levels in FL periods (self-FL) were markedly increased compared to those in non-FL periods (self-non-FL) of the same patients. PL sFas and sFasL levels constituted possible predictors of disease activity concerning FL in patients with SLE.	P: 56 (total SLE), 28 [with FL (FL)] [all f; (Mn: 46.9, SD: 14.0)], 28 (non-FL) [all f; (47.2, 12.3)], C: 28 [healthy controls (HC)] [all f; (46.8, 13.5)], measurement time-points: baseline (BS), non-FL and FL periods of the same patients	PL (sFas/sFasL, pg/ml), MPAA (Mn, SEM): [SLE-BS: FL (ca. 120/ca. 460, ca. 33/ca. 50), non-FL (ca. 14/ca. 200, ca. 5.8/ca. 23)], [SLE: self-FL (ca. 80/ca. 510, ca. 22/ca. 89), self-non-FL (ca. 27/ca. 100, ca. 8.4/ca. 33)]; $p < 0.001$/$p < 0.001$ (FL-BS vs non-FL-BS), p = ns/$p < 0.001$ (self-FL vs self-non-FL)	[96]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFasL, autoimmune lymphoproliferative syndrome (ALPS)	Serum (SR) sFasL levels in patients with ALPS were considerably higher than those in healthy mutation-positive relatives (HMPR). SR sFasL levels may be used to diagnose patients with ALPS with deleterious heterozygous *FAS*-gene mutations prior to molecular testing.	P: 150 (total ALPS) [onset (Md: 2.7, Iqr: 0.8–5.5); first clinical visit (15.4, 8.5–28.0)], 78 [probands (PB)] (52 m/53 f), 72 [relatives (RE)] (45 m/27 f), C: 63 (HMPR) [23 m/40 f; (46, 5–92)]	SR (sFasL, pg/ml), ELISA (Md, Iqr): [total ALPS (1146, 581–1995)], [ALPS: PB (1478, 870–2692), RE (837, 341–1394)], [HMPR (306, 208–1414)]	[97]
sFas and sFasL, rheumatoid arthritis (RA)	Serum (SR) sFas and sFasL levels were not significantly different between patients with anti-TNFα-treatment (ATNF)-naïve RA and healthy controls (HC). After three months of ATNF, SR sFas, but not sFasL, levels in patients with RA were significantly increased compared to those in untreated patients with RA and HC. SR sFas levels in patients with RA with clinical remission (CR) were significantly higher than those in improved patients without CR. SR sFas level might be used as a potential biomarker regarding RA disease activity.	P: 52 (total RA) [15 m/37 f; (Mn: 52.1, SD: 16.6)], measurement time-points: before (BE) and after 3 months (3M) of ATNF with adalimumab (ADA) or infliximab (IFX), C: 40 (HC) [12 m/28 f; (age-matched)]	SR (sFas/sFasL, pg/ml), ELISA(Md, Iqr): [RA: BE (5248.7/48.4, 5079.4–5602.5/43.9–57.8), total 3M-ATNF (9580.1/51.6, 7597.7–10759.1/37.5–64.8)], [HC (5566.0/50.4, 4755.2–5973.5/38.0–59.0)], sFas: [RA: 3M-ADA (9580.1, 7597.7–10652.0), 3M-IFX (9541.9, 7007.7–10925.5), CR (10677.5, 9584.9–11313.6), non-CR (8080.9, 6339.3–9160.6)]; p = ns/p = ns (RA-BE vs HC), sFas: $p < 0.001$ (RA: total 3M-ATNF, 3M-ADA, 3M-IFX vs RA-BE, HC; RA: CR vs non-CR)	[98]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
DcR3, Sjögren's syndrome (SS) (primary)	Serum (SR) DcR3 levels in patients with primary Sjögren's syndrome (SS) were significantly higher than those in healthy controls (HC). SR DcR3 levels were significantly elevated in patients with new-onset SS (NEO) compared with other patients with SS (non-NEO) and significantly decreased after treatment with disease-modifying anti-rheumatic drugs (DMARD). DcR3 levels positively correlated with SS disease activity index (SSDAI) and SS disease damage index (SSDDI), but showed no significant correlation with autoantibodies against cell nuclei (ANA) level.	P: 107 (total SS) [10 m/97 f; (Mn: 50.9, SD: 14.9, Rg: 18–81)], 27 (NEO) [2 m/25 f; (49.1, 14.4, 19–78)], 80 (non-NEO) [8 m/72 f; (48.6, 15.6, 18–81)], C: 20 (HC) [3 m/17 f; (38, 3, 23–76)], measurement time-points: before (BE) and after (AF) DMARD treatment (SS, n = 10)	SR (DcR3, pg/ml), ELISA (Mn, SD): [SS: NEO (774.0, 478.6), non-NEO (566.9, 340.8)], [HC (229.3, 242.5)]; $p < 0.0001$ (SS-non-NEO vs HC), $p = 0.036$ (SS: NEO vs non-NEO), $p = 0.042$ (SS-DMARD: BE vs AF), Corr. (vs DcR3): $p = 0.005$, $r = 0.284$ (SSDAI), $p < 0.001$, $r = 0.366$ (SSDDI), $p = 0.587$, $r = 0.056$ (ANA)	[99]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
DcR3, rheumatoid arthritis (RA) with/without rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (CCPAb), or interstitial lung disease (ILD)	Serum (SR) DcR3 levels were significantly higher in patients with rheumatoid arthritis (RA) than the levels in those with osteoarthritis (OA) and healthy controls (HC). Synovial fluid (SF) DcR3 levels were higher than SR DcR3 levels in patients with RA. SR DcR3 levels before TNF-α blockage treatment (TNFBL) were significantly higher than those after 16 weeks of TNFBL. SR DcR3 levels did not significantly correlate with clinical features in RA, including the presence of RF, CCPAb, or ILD. SR and SF DcR3 levels may be of therapeutic importance in patients with RA.	P: 145 (total RA) [22 m/123 f; (Mn: 57.1, SD 16.9)], C: 40 (OA) [nd; (nd, nd)], 85 (HC) (gender- and age-matched), RA (n = 21) patients (21RA) were selected for comparison DcR3 levels in SR (SR) and synovial fluid (SF), measurement time-points [RA (n = 35) (35RA)]: before (BE) and after 16-weeks TNFBL (16W)	SR and SF (DcR3, pg/ml), ELISA (Mn, SD): [SR: total RA (1114.7, 45.27), OA (498.1, 51.5), HC (450.4, 19.9)], [21RA: SR (1354.1, 169.4), SF (2030.3, 230.8)], [35RA-SR-TNFBL: BE (1296.1, 132.8), 16W (687.8, 63.1)], [total RA: RF+ (Md: ca. 1000), RF- (ca. 1000); CCPAb+ (ca. 1100), CCPAb- (ca. 1000); ILD+ (ca. 1100), ILD- (ca. 1000)]; $p < 0.0001$ (SR: total RA vs OA, HC; 35RA-SR-TNFBL: BE vs 16W), $p = 0.003$ (RA: SF vs SR), total RA: $p = 0.335$ (RF+ vs RF-), $p=0.078$ (CCPAb+ vs CCPAb-), $p=0.230$ (ILD+ vs ILD-)	[100]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFasL, nephrotic syndrome (NS) with focal segmented glomerulonephritis (FSGS), (pediatric)	Serum (SR) sFasL levels in patients with pediatric NS were significantly higher than those in healthy controls (HC). A significant increase in SR sFasL levels in patients with NS with FSGS was observed compared to those with NS with minimal change in glomerulonephritis (MCGN). SR sFasL levels could be used as a non-invasive alternative to kidney biopsy and may improve diagnostic accuracy in the assessment of pediatric NS.	P: 30 (total NS) [16 m/14 f; (Mn: 9.9, SD: 3.88)], 18 (FSGS), 12 (MCGN), C: 24 (HC) [12 m/12 f; (10, 4.51)]	SR (sFasL, pg/ml), ELISA (Mn, SD): [total NS (183.29, 43.34)], [HC (99.28, 7.20)], [NS: FSGS (145.95, 26.34), MCGN (90, 1.09)]; $p = 0.000$ (total NS vs HC), $p = 0.004$ (NS: FSGS vs MCGN)	[101]
DcR3, renal vasculitis (RV) associated with myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA)	No statistically significant difference in the mean serum (SR) DcR3 was observed between patients with total MPO-ANCA-associated renal vasculitis (MPO-AAV) and total non-MPO-AAV controls. However, SR DcR3 levels in patients with active MPO-AAV were significantly higher than the levels in those with inactive and non-MPO-AAV controls. SR DcR3 levels may be a useful marker for disease activity in patients with MPO-AAV.	P: 48 (total MPO-AAV), 24 [with active vasculitis before initial treatment (ACT)] [13 m/ 11 f; (Mn: 71.0, SD: 14.8)], 24 [inactive vasculitis during remission (INACT)] [13 m/11 f; (68.2, 14.2)], C: 20 (non-MPO-AAV) [12 m/8 f; (69.6, 12.3)], (6 healthy controls, 14 chronic kidney diseases patients)	SR (DcR3, ng/ml), ELISA (Mn, SD): [total MPO-AAV (1.89, 3.01)], [total non-MPO-AAV (0.74, 0.46)], [MPO-AAV: ACT (ca. 3.2, ca. 3.9), INACT (ca. 0.9, ca. 0.7)]; $p = 0.0963$ (total MPO-AAV vs total non-MPO-AAV), $p < 0.0001$ (MPO-AAV-ACT vs MPO-AAV-INACT, total non-MPO-AAV)	[102]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
DcR3, asthma (AS) with/without atopy (AT) (adult)	Serum (SR) DcR3 levels in adult patients with AS were significantly higher than those in healthy controls (HC). SR DcR3 levels in patients with AS patients with AT (AS-AT) were not statistically different from those patients with non-atopic AS (AS-non-AT). Significant correlations of SR DcR3 levels with total eosinophil count (TEC), % of the predicted value for forced expiratory volume in 1 sec (pFEV1%), % of predicted FEV1 divided by forced vital capacity (pFEV1/FVC%), and asthma control test score (ACTS) were observed in AS-non-AT, but not in AS-AT. SR DcR3 levels were suggested to be a potent biomarker for the prediction of disease severity in AS-non-AT.	P: 70 (total AS) [43 m/27 f; (Mn: 53.8, SD: 14.2)], 37 (AT) [24 m/13 f; (49.6, 14.3)], 33 (non-AT) [19 m/14 f; (58.6, 12.6)], C: 20 (HC) [12 m/8 f; (51.3, 9.9)]	SR (DcR3, pg/ml), ELISA (Mn, SD): [total AS (266.1, 60.6)], [HC (63.7, 21.9)], [AS: AT (298.7, 111.2), non-AT (230.6, 38.5)]; $p = 0.003$ (total AS vs HC), $p = 0.064$ (AS: AT vs non-AT), Corr. (vs DcR3, AS-AT/AS-non-AT): $p = 0.988$/$p = 0.012$, $r = 0.003$/$r = 0.448$ (TEC), $p = 0.231$/$p = 0.018$, $r = -0.211$/$r = -0.409$ (pFEV1%), $p = 0.791$/$p = 0.021$, $r = 0.047$/$r = -0.399$ (pFEV1/FVC%), $p = 0.428$/$p = 0.003$, $r = -0.141$/$r = -0.505$ (ACTS)	[103]
sFasL, bullous pemphigoid (BP)	Blister fluid (BF) sFasL levels in patients with BP were significantly higher than those in serum (SR) sFasL. sFasL was not detected in both healthy controls (HC) samples.	P: 24 (BP) [6 m/18 f; (Rg: 61–95)], 14 (sFasL measured), C: 10 (HC) (nd/nd; nd-nd)]	SR and BF (sFasL, ng/ml); ELISA (Mn, SEM): [BP: SR (ca. 1.1, ca. 0.34), BF (ca. 3.7, ca. 0.80)], [HC: SR or BF (not detectable)]; $p < 0.01$ (BP: SR vs BF)	[104]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, anti-N-methyl-D-aspartate receptor encephalitis (AMARE)	Cerebrospinal fluid (CSF) sFas and sFasL levels in patients with AMARE were significantly higher than those in patients with encephalitis of other causes (EOC) or peripheral neuropathy (PN). Serum (SR) sFas and sFasL levels in patients with AMARE were significantly higher than the levels in those with PN, but not in patients with EOC. CSF, but not SR, levels of sFas and sFasL significantly correlated with disease activity six months after onset of symptom assessed by the modified Rankin scale (mRS). CSF sFas and sFasL levels may be sensitive markers for disease severity in patients with AMARE.	P: 24 (AMARE) [10 m/14 f; (Mn: 39.58, SD: 17.51), C: 24 (non-AMARE), 13 (EOC) [5 m/8 f; (39, 18.93)], 11 (PN) [6 m/5 f; (45.64, 13.82)], measurement time-points: the most critical time of disease and 6 months (6M) after symptom onset	CSF and SR (sFas/sFasL, pg/ml); ELISA (Mn, SD): [AMARE: CSF (ca. 170/ca. 110, ca. 28/ca. 21), SR (ca. 770/ca. 270, ca. 150/ca. 61)], [EOC: CSF (ca. 110/ca. 67, ca. 23/ca. 16), SR (ca. 570/ca. 220, ca. 190/ca. 55)], [PN: CSF (ca. 93/ca. 58, ca. 13/ca. 9.0), SR (ca. 470/ca. 150, ca. 100/ca. 46)]; p = 0.0020/0.0120 (CSF: AMARE vs EOC), p = 0.0005/0.0034 (CSF: AMARE vs PN), p = 0.1932/0.3926 (SR: AMARE vs EOC), p = 0.0184/0.0116 (SR: AMARE vs PN), Corr. (vs: CSF sFas/sFasL) p = 0.0025/p = 0.019, r = 0.5875/r = 0.4748 (mRS at 6M)	[105]
sFas and sFasL, juvenile dermatomyositis (JDM) (pediatric, adolescent)	Serum (SR) sFas and sFasL levels in patients with JDM and juvenile idiopathic arthritis (JIA) did not show a statistically significant difference from those in healthy controls (HC).	P: 22 (JDM) [all f; (Md: 9.9, Rg: 3.4–20.8)], C: 20 (JIA) [all f; (12.5, 3.8–19.2)], 26 (HC) [all f; (10.9, 2.1–20.3)]	SR (sFas/sFasL, sFas: pg/ml, sFasL: ng/ml), ELISA (Md): [JDM (ca. 110/ca. 0.32)], [JIA (ca. 180/ca. 0.20)], [HC (ca. 110/ca. 0.30)]; p = 0.1/p = nd (among JDM JIA, HC), p = 0.6/p = nd (JDM vs HC), p = 0.06/p = 0.3 (JIA vs HC)	[106]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas, systemic lupus erythematosus (SLE) with/without coronary artery disease (CVD) or carotid plaque (CP)	Plasma (PL) sFas levels in patients with SLE with prevalent coronary artery disease (CVD) or carotid plaques (CP) were significantly higher than those in patients without them. Patients with SLE with elevated PL sFas levels had a higher risk of permanent organ damage assessed as a higher Systemic Lupus International Collaborating Clinics damage index (SDI). PL sFas levels may be a biomarker reflecting disease severity in patients with SLE.	P: 470 (total SLE), 69 [with CVD (CVD)] [36 m/63 f; (Md: 56.8, Rg: 49.5–66.1)], 401 (non-CVD) [60 m/341 f; (43.9, 31.9–56.1)], 60 [with CP (CP)], 236 (non-CP), C: 253 (non-SLE) (age- and gender-matched to SLE patients)	PL (sFas, pg/ml), MPAA (PEA) (Md, Rg): [SLE: CVD (209, 162–272), non-CVD (177, 141–229); CP (220, 170–270), non-CP (174, 134–222)]; p = 0.004 (SLE: CVD vs non-CVD), p < 0.001 (SLE: CP vs non-CP), risk analysis for co-existing diseases and disease severity (sFas, adjusted for gender and age): OR = 1.44 (95% CI: 0.87–2.38) (CVD), OR = 2.46 (95% CI: 1.31–4.60) (CP), OR = 2.34 (95% CI: 1.60–3.43) (SDI > 1)	[107]
sFasL, autoimmune lymphoproliferative syndrome (ALPS)	A significant difference in plasma (PL) sFasL levels was observed between patients with definite ALPS (ALPS-DEF) and those with unlikely ALPS (ALPS-UNL), but not between patients with ALPS-DEF and suspected ALPS diagnosis (ALPS-SUS). PL sFasL levels in patients with ALPS with *FAS* gene mutation (*FAS*-m) were significantly higher than the levels in those with ALPS with unknown gene mutation (*UNK*-m).	P: 215 (total possible ALPS) [132 m/83 f; (Md: 12.3, Rg: 0.083–76)], 140 (total patients with sufficient data to define diagnosis), 38 (ALPS-DEF) [nd/nd; (9.3, 0.33–77)], 17 (ALPS-SUS) [nd/nd; (13.1, 0.083–19)], 85 (ALPS-UNL) [nd/nd; (10.3, 0.17–64)]	PL (sFasL, pg/ml), ELISA (Md, Iqr): [ALPS: DEF (195, 44– >1000), SUS (154, 23.5-939), UNL (139, 35– >1000)], ALPS-DEF/SUS: [ALPS: *FAS*-m (>1000, 128.9– >1000), *UNK*-m (152, 23.5–486)]; p = 0.013 (ALPS: DEF vs UNL), p = 0.0674 (ALPS: DEF vs SUS), p < 0.0001 (ALPS-DEF/SUS: *FAS*-m vs *UNK*-m)	[108]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, multiple sclerosis (MS) (relapsing-remitting)	Serum (SR) sFas, but not sFasL, levels were significantly higher than cerebrospinal fluid (CSF) levels in patients with relapsing-remitting MS (RRMS). Neither SR sFas nor sFasL levels were significantly affected by corticosteroid therapy (CT). Both SR sFas and sFasL levels in patients with RRMS with antinuclear antibody (ANA) were significantly higher than the levels in those with ANA-negative. SR sFasL, but not sFas, levels in patients with RRMS showed a significantly negative correlation with patients' expanded disability status scale (EDSS) scores.	P: 44 (total RRMS) [12 m/32 f; (total: Mn: 38.43, SD: 10.25, m/f: 33.91, 9.72/40.12, 10.07)], 19 [with ANA-positive (ANA)], 25 (non-ANA), measurement time-points: before (BE, n = 16) and 24 h after initiation of CT (24H, n = 28)	SR (n = 44) and CSF (n = 11) (sFas/sFasL, pg/ml), MPAA (Md, Iqr) or (Mn, SD): [total RRMS: SR (130.21/4.06, 48.02–468.95/0.00–20.66), CSF (1.50/1.69, 0.84–2.15/1.12–2.82); BE-CT (104.12/12.01, 24.48–403.56/0.00–25.58), 24H-CT (215.20/2.86, 52.64–670.25/0.00–5.76)], [RRMS-SR: ANA (437.83/18.20, 376.79/3.12–23.45), non-ANA (208.67/1.00, 251.94/0.00–9.44)]; $p < 0.001$/$p = 0.43$ (total RRMS: SR vs CSF), $p = 0.37$/$p = 0.46$ (total RRMS-CT: BE vs 24H), $p = 0.02$/$p = 0.02$ (RRMS-SR: ANA vs non-ANA), Corr. (vs sFas/sFasL): $p = 0.14$/$p = 0.006$, $r_s = -0.227$/$r_s = -0.405$ (vs EDSS score)	[109]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, systemic lupus erythematosus (SLE)	Serum (SR) sFas and sFasL levels in patients with SLE were significantly higher than those in healthy controls (HC). SR sFas and/or sFasL levels were significantly associated with longitudinal risks of some clinical outcomes (CO), including time-adjusted mean SLE disease activity index 2000 (AMS) and flare over time (FLO).	P: 118 (SLE) [18 m/100 f; (Mn: 45.4, SD: 14.2)], C: 17 (HC) [gender-matched; (37.4, 10.2)]	SR (sFas/sFasL, pg/ml), MPAA (Mn, SD): [SLE (ca. 10000/ca. 44, ca. 1400/ca. 3.6), [HC (ca. 7200/ca. 37, ca. 690/ca. 4.8); $p < 0.01$/$p = 0.04$ (SLE vs HC), risk analysis for CO (sFas/sFasL: ≤ Md vs > Md): $p < 0.01$/$p = 0.69$, OR = 3.01/OR = 0.86 (AMS >4), $p < 0.01$/$p = 0.03$, OR = 4.38/OR = 0.4 (FLO)	[110]
DcR3, asthma (AS) with/without atopy (AT) (pediatric)	Serum (SR) DcR3 levels in pediatric patients with AS were significantly higher than those in healthy controls (HC). However, no significant difference in SR DcR3 levels was observed between AS with AT and AS without AT. SR DcR3 levels significantly correlated with the asthma control test score (ACTS) in patients with AS with AT, but not in those with total AS. SR DcR3 levels could be a promising prognostic biomarker for disease activity in pediatric patients with atopic AS.	P: 60 (total AS) [34 m/26 f; (Mn: 8.9, SD: 2.0)], 28 (AT) [16 m/12 f; (9.0, 1.9)], 32 (non-AT) [18 m/14 f; (8.9, 2.1)], C: 25 (HC) [9 m/16 f; (9.0, 2.4)]	SR (DcR3, pg/ml), ELISA (Md, Rg): [total AS (4502, 3430–10800)], [HC (3506, 3188–4210)], [AS: AT (4797, 3038–14870), non-AT (4390, 3602–9915)]; $p = 0.007$ (total AS vs HC); $p = 0.947$ (AS: AT vs non-AT), Corr. (vs DcR3, in AS-AT/total AS): $p = 0.039$/$p = 0.202$, $r = -0.392$/$r = -0.167$ (ACTS)	[111]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFasL, hemophagocytic lymphohistiocytosis (HLH) (primary, secondary), juvenile idiopathic arthritis (JIA)-macrophage activation syndrome (MAS)	Serum (SR) sFasL levels in patients with primary (PRI) and secondary (SEC) HLH were significantly higher than the levels in those with systemic (SYS) JIA-MAS and healthy controls (HC). SR sFasL level was selected as a potential biomarker for discrimination in the validation cohort (VC) from data analysis in the discovery cohort (DC). SR sFasL level was able to significantly discriminate SYS-JIA-MAS from PRI-HLH or total HLH, but not from SEC-HLH, in VC.	[DC], P: 72 (total HLH), 28 (PRI-HLH) [14 m/14 f; (Md: 1.0, Rg: 0.1–4.2)], 44 (SEC-HLH) [21 m/23 f; (8.9, 0.7–17.8)], 40 (SYS-JIA-MAS), [25 m/15 f; (10.7, 2.3–17.8)], C: 10 (HC) [4 m/6 f; (11.0, 6.0–18.0)]; [VC], P: 18 (PRI-HLH), 32 (SEC-HLH), 27 (SYS-JIA-MAS)	SR (sFasL in DC, pg/ml), MPAA (Md): [HLH: PRI (ca. 200-ca. 300), SEC (ca. 100–ca. 200)], [SYS-JIA-MAS (ca. 7–ca. 8)], [HC (ca. 1–ca. 2)]; p = 0.0002 (PRI-HLH vs HC), p = 0.0001 (SEC-HLH vs HC), p = 0.0023 (PRI-HLH vs SYS-JIA-MAS), p = 0.0015 (SEC-HLH vs SYS-JIA-MAS), ROC curve analysis for discrimination from SYS-JIA-MAS (sFasL in VC): p = 0.0426, AUC = 0.617 (total HLH), p = 0.0074, AUC = 0.692 (PRI-HLH), p = 0.309, AUC = 0.566 (SEC-HLH)	[112]
DcR3, Kawasaki disease (KD)	Serum (SR) DcR3 levels in patients with KD before intravenous immunoglobulin (IVIG) treatment were significantly higher than those in healthy controls (HC). SR DcR3 levels in patients with KD gradually decreased over time after IVIG treatment. No statistically significant variation in SR DcR3 levels was observed owing to the difference in either IVIG-responding status or coronary artery z-score status.	P: 71 (total KD) [50 m/21 f; (Mn: 3.2, Rg: 2.7–3.7)], C: 66 (HC) [33 m/33f; (2.8, 2.3–3.4)], IVIG treatment response-status: 63 responders (RES), 8 (non-RES), coronary artery z-score status: 9 [>2.0 (CAL)], 62 (non-CAL), measurement time-points: pre- IVIG (PRE), post-IVIG (POST), and one month after IVIG (1M)	SR (DcR3, ng/ml), ELISA (Mn, 95 %CI): [KD: PRE (2.62, 2.51–2.74); POST (2.30, 2.20–2.40); 1M (2.05, 1.96–2.14)], [HC (1.76, 1.67–1.84)]; p < 0.01 (KD-PRE vs KD-POST, KD-1M, HC; KD-POST vs KD-1M, HC; KD-1M vs HC), p = ns (KD-PRE, KD-POST, KD-1M: RES vs non-RES), p = ns (KD: CAL vs non-CAL)	[113]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFasL, allergic diseases (ALD) (atopy, house-dust mite sensitization, asthma, allergic rhinitis, atopic dermatitis, expiratory airway obstruction) (pediatric)	Cord blood (CB) sFasL levels in 7 year-old (7-yo) patients with ALD symptoms, atopy (AT), sensitization with a house-dust mite, *Dermatophagoides pteronyssinus* (SE), allergic rhinitis (AR), and airway obstruction evaluated by the highest forced expiratory volume in 1 sec/forced vital capacity (FEV1/FVC) < 90% criteria (EAO), but not with asthma (AS) and atopic dermatitis (AD) were significantly higher than those in the patients without them. Infants with elevated CB sFasL levels had significantly higher risks for AT, AR, SE, and EAO. CB sFasL levels at birth might be useful as a biomarker for the prediction of allergic diseases development at 7-yo.	P and C: 258 (enrolled cohort) [131 m/127 f; (gestational age: Mn: 38.1 weeks, SD: 1.7 weeks)], 132 (measured at 7-yo) [72 m/50 f; (38.1 weeks, 1.8 weeks)], 60 [with AT (AT)], 38 (non-AT); 59 [with SE (SE)], 39 (non-SE); 6 [with AS (AS)], 98 (non-AS); 61 [with AR (AR)], 43 (non-AR); 6 [with AD (AD)], 98 (non-AD); 35 [with EAO (FEV1/FVC < 90 %) (EAO)], 90 (non-EAO)	CB (sFasL, pg/ml), ELISA (Mn, SD): [ALD at 7-yo: AT (134.8, 119.4), non-AT (79.3, 39.3); SE (124.1, 112.3), non-SE (77.3, 29.1); AS (71.8, 21.7), non-AS (108.0, 93.0); AR (121.8, 109.0), non-AR (83.3, 48.3); AD (189.4, 206.6), non-AD (100.8, 78.1); EAO (140.1, 131.2), non-EAO (85.8, 51.1)]; p = 0.003 (AT vs non-AT; SE vs non-SE), p = 0.016 (AR vs non-AR), p = 0.022 (EAO vs non-EAO), p = 0.345 (AS vs non-AS), p = 0.343 (AD vs non-AD), risk analysis for ALD at 7-yo (every 100 pg/ml increase in CB sFasL): p = 0.003, OR = 4.56 (AT), p = 0.02, OR = 2.41 (AR), p = 0.02, OR = 2.85 (SE), p = 0.006, OR = 2.11 (EAO)	[114]

The levels of sFas, sFasL, or DcR3 have been widely investigated in patients with Graves' disease (GD) [80,81], Sjögren's syndrome (SS) [79,99], and multiple sclerosis (MS) [90,109]. In patients with Graves' ophthalmopathy (GO), SR sFas levels strongly depended on the symptomatic status of diplopia or extraocular muscle hypertrophy. Patients with GO lacking these symptoms had significantly lower SR sFas levels than those in patients who possessed them and healthy controls [80]. SR sFas and sFasL levels in patients with Graves' hyperthyroidism (GH) with high levels of thyroid-stimulating hormone receptor antibodies (TRAb) were significantly elevated compared to those in drug-treated patients with low TRAb levels and healthy controls. The SR sFas levels changed along a wide range with the TRAb levels, including the low TRAb level region, indicating the usefulness of SR sFas levels as a marker for evaluating aggression or regression in GH [81]. SR sFas and DcR3 levels in patients with SS have been significantly higher than those in healthy controls [79,99]. The SR DcR3 levels were considerably higher in the new-onset cases than those in other SS patients, and the DcR3 levels significantly decreased in correlation with SS disease activity and damage indices after treatment with anti-rheumatic drugs [99]. In contrast, the differences in SR sFas and sFasL levels between patients with MS and healthy controls as well as that between patients with relapsing-remitting MS (RRMS) in CR and those during relapse were relatively small [90]. In addition, the difference in SR sFas or SR sFasL levels before and after corticosteroid therapy reached statistical significance; however, both the sFas and sFasL levels were found to be significantly elevated in patients with RRMS associated with the antinuclear antibody, compared to those of cases without it [109].

Although still limited to a single study, sFas, sFasL, and DcR3 levels in body fluids have been examined for their possible usage as clinical biomarkers in numerous autoimmune diseases [79,82,83,85,91,101,102,104–106,112,113]. The mean SR sFas levels in patients with systemic sclerosis and polymyositis/dermatomyositis were slightly higher than those in healthy controls, but significantly lower than those in patients with SLE [79]. SR sFas levels in patients with chronic hepatitis exhibiting autoimmune features [82], SR sFasL levels in patients with pediatric nephrotic syndrome [101], primary and secondary hemophagocytic lymphohistiocytosis [112], and blister fluid sFasL levels in patients with bullous pemphigoid [104] were significantly higher than those in the non-autoimmune type or healthy controls. In contrast, SR sFas levels in patients with familial Mediterranean fever and amyloidosis were significantly lower than those in patients without amyloidosis or in healthy controls [83]. Both SR sFas and sFasL levels in juvenile dermatomyositis or juvenile idiopathic arthritis patients [106] and SR sFas levels in silicosis patients with autoimmunity alterations [85] were not significantly different from those in healthy controls. Regarding the difference in disease activity, a significant increase was observed in SR sFasL levels in patients with nephrotic syndrome accompanied by focal segmented glomerulonephritis [101] and in SR DcR3 levels in patients suffering from active renal vasculitis associated with myeloperoxidase-antineutrophil cytoplasmic antibody [102] compared to that in patients with less severe or inactive disease. However, neither SR sFas nor SR sFasL levels in patients with collagen diseases in the acute-onset interstitial lung disease state were significantly different from those in stable state [91]. SR DcR3 levels in patients suffering from an autoimmune disease-related pediatric acute febrile systemic vasculitis, Kawasaki disease (KD) were significantly higher than those in healthy controls [113]. DcR3 levels in patients with KD gradually decreased over time after standard intravenous immunoglobulin treatment.

Studies targeting sFasL and DcR3 levels in patient body fluids have also been performed for allergic diseases [103,111,114]. SR DcR3 levels were not significantly different between atopic and non-atopic asthma patients in either adult or pediatric patients [103,111]. However, DcR3 levels of

adults and pediatric asthma patients correlated significantly with the disease activity index named asthma control test score, only in the non-atopic and atopic cases, respectively. Cord blood (CB) sFasL levels at birth were identified as a useful predictive biomarker for the onset of allergic diseases in children aged 7 years [114]. Infants with elevated CB sFasL levels had significantly higher risks of atopy, sensitization with a house dust mite, allergic rhinitis, and expiratory airway obstruction, but not that of asthma or atopic dermatitis.

3.3. Infectious diseases [115–158]

3.3.1. Septic diseases caused by bacterial infections [115–131]

The possible use of sFas, sFasL, and DcR3 as clinical biomarkers has been investigated for various septic diseases caused by bacterial infections (Table 3). SR/PL sFas levels in sepsis/bacteremia and cerebrospinal fluid (CSF) DcR3 levels in bacterial meningitis patients showed a consistent statistically significant elevation compared with those in healthy controls [115–117,119–122,125–128,130]. SR/PL sFas and SR DcR3 levels were commonly correlated with disease severity, as determined by the sequential organ failure assessment (SOFA) [115,116,118] and acute physiology and chronic health evaluation (APACHE) II [117,125] scores, respectively. SR DcR3 levels may be efficient diagnostic biomarkers for the discrimination of sepsis from other non-infectious diseases exhibiting similar clinical symptoms, including systemic inflammatory response syndrome (SIRS), with high sensitivity and specificity [119,125,128,130]. This diagnostic efficiency was further enhanced by combining it with conventional biomarkers for sepsis such as soluble urokinase-type plasminogen activator receptor, procalcitonin [128], and C-reactive proteins [130]; however, the statistical significance was lost when postmortem SR samples were used as test specimens [129]. SR DcR3 levels in patients with sepsis [130], but not CSF DcR3 levels in patients with bacterial meningitis [120], discriminated between Gram staining types of causative bacterial strains. The SR sFasL levels in patients with sepsis largely depended on the case regarding the existence and outcome of the disease [115,118,122,123], and the sFas/sFasL ratio rather than the sFasL level alone was a better marker for disease severity [118,122]. PL sFasL expression levels were useful for discriminating mono- from polymicrobial necrotizing soft-tissue infections [131].

Table 3. Possible usage of sFas, sFasL, and DcR3 as clinical biomarkers in infectious diseases, excluding cancers, autoimmune, and allergic diseases.

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
sFas and sFasL, sepsis (SP)	Serum (SR) sFas and sFasL levels in patients with severe SP (SEV-SP) were significantly higher than those in patients with non-severe SP (non-SEV-SP) and healthy controls (HC). The difference in both SR sFas and sFasL levels between SEV-SP and non-SEV-SP patients was most evident on 3 days after hospitalization during a 15-day observation period. SR sFas levels were significantly lower in survivors (SUV) than those in non-survivors (non-SUV). SR sFas levels in patients with SP and sequential organ failure assessment (SOFA) score had a direct positive relationship. SR sFas levels could serve as a potential marker of severity in patients with SP.	P: 14 (total SEV-SP) [9 m/5 f; (Mn: 45.6, SD: 17)], 6 (SUV) [4 m/2 f; (33, 15)], 8 (non-SUV) [5 m/3 f; (55, 12)], 8 (total non-SEV-SP) [4 m/4 f; (36.9, 13.2)], SOFA score: 0 (S-I), 1-9 (S-II), >10 (S-III), C: 6 (HC) [3 m/3 f; (37, 12.1)], measurement time-points: baseline (BS), 1 day (1D), 3 day (3D), 8 day (8D), and 15 day (15D) after hospitalization	SR (sFas/sFasL, pg/ml), ELISA (Mn, SEM): [total SEV-SP: 1D (ca. 265/ca. 194, ca. 29/ca. 62), 3D (ca. 334/ca. 256, ca. 46/ca. 100), 8D (ca. 228/ca. 158, ca. 21/ ca. 31), 15D (ca. 199/ca. 125, ca. 39/ca. 26)], [total non-SEV-SP: 1D (ca. 156/ca. 144, ca. 26/ca. 34), 3D (ca. 129/ca. 107, ca. 8.9/ca. 19), 8D (ca. 161/ca. 124, ca. 17/ca. 24)], [HC-BS (118/31.88, 15/12.12)], sFas: [SEV-SP-SUV: 1D (214.1, 34.0), 3D (255.3, 36.1)], [SEV-SP-non-SUV: 1D (328.4, 46.9), 3D (494.1, 83.1)]; $p < 0.01$/$p < 0.05$ (total SEV-SP vs total non-SEV-SP, HC-BS), sFas: $p < 0.05$ (SEV-SP-D1: SUV vs non-SUV), $p < 0.01$ (SEV-SP-D3: SUV vs non-SUV), $p < 0.0001$ (total SP: S-II, S-III vs S-I), $p < 0.001$ (total SP: S-III vs S-II)	[115]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
sFas and sFasL, major trauma (MT) with/without sepsis (SP)	Serum (SR) sFas, but not sFasL, levels in patients with MT who developed SP were significantly elevated at 1, 5, and 9 days after injury, compared with those in healthy controls (HC) and those with MT who recovered without SP at day 5 and 9. SR sFas levels exhibited a strong positive correlation with organ dysfunction scores, including the sequential organ failure assessment (SOFA) scoring. sFas levels may be a therapeutic target to prevent post-trauma hyperinflammation and SP.	P: 47 (total MT) [31 m/16 f; (Mn: 45.9, SEM: 2.9, Rg: 20–96)], 18 [with sepsis after injury (SP)] [15 m/3 f; (53.5, 4.6, 20–78)], 29 (non-SP) [nd/nd; (41.1, 4.4, nd)], C: 17 (HC) (nd/nd; nd), measurement time-points: 1 day (1D), 5 days (5D), 9 days (9D) after major trauma	SR (sFas/sFasL, pg/ml), ELISA (Md): [MT-SP: 1D (122.5/ca. 110), 5D (230/ca. 80), 9D (187.1/ca. 70)], [MT-non-SP: 1D (101.6/ca. 82), 5D (86.46/ca. 54), 9D (68.95/ca. 59)], [HC (70.29/ca. 77)]; sFas (MT-SP vs HC): $p < 0.05$ (1D), $p < 0.001$ (5D), $p < 0.01$ (9D), sFas (MT: SP vs non-SP): p = ns (1D), $p < 0.01$ (5D), $p < 0.05$ (9D), Corr. (sFas vs SOFA score) in MT-SP: $p < 0.001$, $r = 0.7$ (1D), $p < 0.01$, $r = 0.62$ (5D), $p < 0.01$, $r = 0.58$ (9D)	[116]
DcR3, sepsis (SP) and systemic inflammatory response syndrome (SIRS)	Serum (SR) DcR3 levels in SP patients were significantly higher than those in SIRS patients and healthy controls (HC). SR DcR3 levels exhibited statistically significant correlations with SP severity assessed by acute physiology and the chronic health evaluation II (APACHE II) score. SR DcR3 level had potentials to serve as a new diagnostic biomarker for SP and SIRS with high specificity and sensitivity.	P: 24 (SP) [15 m/9 f; (Mn: 58.3, SD: 12.7)], 43 (SIRS) [nd/nd; (55.4, 10.6)], C: 118 (HC) [nd/nd; (53.3, 12.1)]	SR (DcR3, ng/ml), ELISA (Mn, SD): [SP (6.11, 2.58)], [SIRS (2.62, 1.46)], [HC (0.91, 0.56)]; $p < 0.0001$ (SP vs SIRS, HC; SIRS vs HC), Corr. (vs DcR3): $p = 0.005$, $r = 0.556$ (APACHE II score), ROC curve analysis for discrimination of diseases (DcR3): $p < 0.0001$, AUC = 0.992 (SP vs HC), $p < 0.0001$, AUC = 0.910 (SIRS vs HC), $p < 0.0001$, AUC = 0.896 (SP vs SIRS)	[117]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
sFas and sFasL, bacteremia (BR) (culprit micro-organisms: *Escherichia coli*, *Staphylococcus aureus*, *Streptomyces pneumoniae*, and β-hemolytic *Streptococcus*)	In patients with BR, plasma (PL) sFas levels decreased and PL sFasL increased after the follow-up time (>25 days). After blood culture, the high sFas levels during the 1–4 days were significantly associated with severe organ dysfunction (SEV) evaluated by the sequential organ failure assessment score (SOFA score), and hypotension (HYP). High sFas/sFasL ratios and low sFasL levels during the same period were also significantly associated with a high SOFA score (SEV). However, maximum sFas levels, maximum sFas/sFasL ratio, and minimum sFasL levels failed to predict case fatality on day 30 (FD-30).	P: 132 (BR) [70 m/62 f; (Md: 62, Rg: 16–93)], measurement time-points: 1–2 days (n = 34) (1–2D), 3 days (n = 82) (3D), 4 days (n = 104) (4D), 13–18 Days (n = 75) (13–18D), >25 days (n = 91) (>25D) after positive blood culture, during 1–4D: 118 [survivors on day 30 (SUV)], 18 (non-SUV); 55 [severe (SOFA score ≥4) (SEV)], 77 (non-SEV); 52 [hypotension (<70 mmHg) (HYP)], 80 (non-HYP); 67 [high maximum sFas level (max-sFas) (≥9650 ng/ml) (H-MF)], 65 [low max-sFas (L-MF)]; 62 [low minimum sFasL (min-sFasL) level (≤ 28.5 ng/ml) (L-MFL)], 70 [high min-sFasL (H-MFL)]; 87 [high sFas/sFasL ratio (≥224) (H-FFR)], 44 [low sFas/sFasL ratio (L-FFR)]	PL (sFas/sFasL, ng/ml), ELISA (Md): [BR: 1–2D (8953/32.3), 3D (9628/32.8), 4D (9467/29.6) 13–18D (8381/41.0), >25D (7998/54.5)], PL (max-sFas/min-sFasL, ng/ml), ELISA (Md): [BR-1-4D: SUV (9594/29.4), non-SUV (10823/27.9); SEV (11046/26.4), non-SEV (8980/33.1); HYP (10939/28.7), non-HYP (9017/30.3)]; max-sFas/min-sFasL: p = 0.100/p = 0.462 (SUV vs non-SUV), p < 0.001/p = 0.003 (SEV vs non-SEV), p = 0.002/p = 0.297 (HYP vs non-HYP), risk analysis for clinical outcomes [HYP; SEV; FD-30]: [p = 0.001, OR = 3.6; p < 0.001, OR = 4.3; p = 0.146, OR = 2.1] (H-MF vs L-MF), [p = 0.039, OR = 2.3; p = 0.001, OR = 4.2; p = 0.102, OR = 2.8] (L-MFL vs H-MFL), [p = 0.574, OR = 1.2; p = 0.004, OR = 2.8; p = 0.432, OR = 1.5] (H-FFR vs L-FFR)	[118]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
DcR3, sepsis (SP) and systemic inflammatory response syndrome (SIRS)	Serum (SR) DcR3 levels in patients with SP were significantly higher than levels in those with SIRS, renal cell cancer (RCC), Crohn's disease (CD), and healthy controls (HC). SR DcR3 levels discriminated SP from SIRS, RCC, and CD with excellent sensitivity and specificity. SR DcR3 levels may serve as a reliable biomarker in SP diagnosis.	P: 25 (SP) [14 m/11 f; (Mn: 65, Rg: 38–97)], 23 (SIRS) [17 m/6 f; (45, 18–84)], C: 124 (non-SP-non-SIRS), (nd/nd; nd), 48 (RCC), 30 (CD), 46 (HC)	SR (DcR3, ng/ml), ELISA (Mn, SD): [SP (10.46, 1.46)], [SIRS (2.06, 0.33)], [RCC (1.09, 0.24)], [CD (3.23, 1.75)], [HC (0.43, 0.081)]; $p < 0.0001$ (SP vs SIRS, RCC, CD), $p = 0.0008$ (SIRS vs RCC), $p = 0.00117$ (SIRS vs CD), $p = 0.2925$ (RCC vs CD), ROC curve analysis for prediction of SP (DcR3): $p < 0.0001$ (vs all below), AUC = 0.958 (vs SIRS), AUC = 0.929 (vs CD), 0.980 (vs RCC), AUC = 0.999 (vs HC)	[119]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
DcR3, bacterial meningitis (BM) (nosocomial)	Cerebrospinal fluid (CSF) DcR3 levels in patients with nosocomial BM were significantly higher than the levels in those with non-bacterial meningitis (non-BM). CSF DcR3 levels may be a valuable predictor for differentiating patients with BM from those with non-BM, but it did not discriminate Gram-positive bacterial infection (GP) from Gram-negative bacterial infection (GN). A combination of CSF DcR3 levels with soluble triggering receptor expressed on myeloid cells-1 (sTERM-1) improved predictive and diagnostic powers for BM.	P: 80 (BM) [57 m/23 f; (Mn: 43.75, SD: 16.46)], C: 43 (non-BM) [25 m/18 f; (42.02, 13.90)]	CSF (DcR3, ng/ml), ELISA (Md, Iqr): [BM (0.646, 0.229–1.514)], [non-BM (0, 0–0.192)]; $p < 0.001$ (BM vs non-BM), $p = 0.338$ (BM: GP vs GN), risk analysis for BM: $p = 0.023$, OR = 3.325 (95% CI: 1.185–9.334) (DcR3 alone), $p < 0.001$, OR = 7.007 (95% CI: 3.576–13.730) (DcR3 and sTERM-1 combined), ROC curve analysis for BM diagnosis: p = nd, AUC = 0.831, (95% CI: 0.752–0.911) (DcR3 alone), $p < 0.001$, AUC = 0.842 (95% CI: 0.770–0.914) (DcR3 and sTERM-1 combined)	[120,121]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
sFas and sFasL, sepsis (SP) with/without shock	Plasma (PL) sFasL levels and sFas/sFasL ratio in patients with severe sepsis (SEV-SP) were significantly lower and higher, respectively, than those in healthy controls (HC). PL sFas levels were higher than those in HC, but without statistical significance. PL sFasL levels and the sFas/sFasL ratio could be candidates for the diagnosis of SEV-SP, and their diagnostic values were not much inferior to the conventional PL procalcitonin (PCT) predictor.	P: 40 (total SEV-SP) [28 m/12 f; (Mn: 74.5, SEM: 2.1)], 12 [with shock (SH)] [7 m/5 f; (69.5, 4.2)], 28 (non-SH) [21 m/7 f; (76.5, 2.3)], C: 35 (HC) [23 m/13 f; (57.6, 1.3)]	PL (sFas/sFasL, pg/ml), ELISA (Mn, SEM): [total SEV-SP (1378.4/41.2, 489.0/4.7)], [HC (946.9/88.1, 417.8/5.8)] [SEV-SP: SH (1356.0/51.4, 610.6/11.1), non-SH (1388.0/36.7, 654.5/4.7)]; $p = ns/p < 0.05$ (total SEV-SP vs HC), ROC curve analysis for SEV-SP diagnosis: AUC = 0.885 (sFasL), AUC = 0.819 (sFas/sFasL ratio), AUC = 0.906 (PCT)	[122]
sFasL, sepsis (SP)-induced multiple organ failure (MOF) with/without typical inflammation phenotypes (IP) (pediatric)	Plasma (PL) sFasL levels were a confirmatory biomarker for patients with pediatric severe SP (SEV-SP)-induced sequential MOF (SEQ-MOF) with hepatobiliary dysfunction phenotype. SEQ-MOF survivors reached PL sFasL levels of <200 pg/ml during the follow-up period, while non-survivors showed >200 pg/ml throughout the follow-up period.	P: 100 (total SEV-SP) [53 m/47 f; (Mn: 5.8, SD: 5.7)], 25 (single organ failure), 75 (total MOF), 38 (MOF without IP), 37 (total MOF with 1-3 IP), 30 (MOF with 1 IP), 6 (MOF with 2 IP), 1 (MOF with 3 IP), IP: 24 (immune paralysis-associated MOF), 15 (thrombocytopenia-associated-MOF), 6 (SEQ-MOF), measurement time-points (MTP): from day 2-day 28 after SP diagnosis (twice weekly)	PL (sFasL, pg/ml), ELISA (Md, Iqr): [SEQ-MOF: SUV (1st MTP: ca. 250, ca. 220–ca. 280), (4th MTP: ca. 130, ca. 78–ca. 190), non-SUV (1st MTP: ca. 320, nd-nd), (2nd MTP: ca. 380, nd-nd)]	[123]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
sFas, systemic inflammatory response syndrome (SIRS) and sepsis (SP)	Plasma (PL) sFas levels were examined as a possible parameter for mortality in derivation cohort (DC), but was not selected as a final component in the two biomarker models that predicted SIRS or SP patients at low risk of death or organ dysfunction in an external validation cohort (VC).	P: 1925 (total SIRS and SP), 888 (DC) [564 m/324 f; (Mn: 56, SD: 16)], 278 [internal test cohort (TC)] [199 m/79 f; (54, 16)], 759 (VC) [487 m/272 f; (61, 18)]	PL (sFas, pg/ml), MPAA; P (Md, Iqr): [DC (11321, 8428–15692)], [TC (8822, 5925–14880)], [VC (10175, 6927–15390)], ROC curve analysis for mortality in DC (sFas): AUC= 0.71, (95% CI: 0.66–0.76)	[124]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
DcR3, sepsis (SP) and systemic inflammatory response syndrome (SIRS)	Serum (SR) DcR3 levels in patients with SP were significantly higher than the levels in those with SIRS and healthy controls (HC). SR DcR3 levels were significantly associated with disease severity and outcome, and well-correlated with acute physiology and chronic health evaluation (APACHE)-II score of patients with SP. SR DcR3 levels discriminated patients with SP from those with SIRS or HC with a diagnostic efficiency equivalent to or better than a commonly used SP marker, SR procalcitonin (PCT), level. SR DcR3 level may be useful for diagnosis at early stages.	P: 134 (total SP) [79 m/55 f; (Mn: 56.7, SD: 20.4)], disease severity: 69 moderate (MOD), 28 severe (SEV), 37 shock (SH), outcome: 93 survived (SUV), 41 non-survived (non-SUV), acute physiology and chronic health evaluation (APACHE)-II score: 54 [<15 (L-APA)], 44 [15-24 (M-APA)], 36 [>25 (H-APA)], 60 (SIRS) [37 m/23 f; (53.8, 18.6)], C: 50 (HC) [27 m/23 f; (47.7, 25.4)]	SR (DcR3, ng/ml), ELISA; P (Md): [total SP (4.25)], [SIRS (1.28)], [HC (0.17)], [SP: MOD (3.22), SEV (5.28), SH (7.49); SUV (3.46), non-SUV (7.46); L-APA (3.03), M-APA (4.58), H-APA (8.05)]; $p < 0.001$ (total SP vs SIRS, HC), $p = 0.003$ (SIRS vs HC), $p < 0.001$ (among SP: MOD, SEV, SH; SP: SUV vs non-SUV; among SP: L-APA, M-APA, H-APA), Corr. (vs DcR3): $p < 0.001$, $r = 0.82$ (APACHE-II score), ROC curve analysis for disease discrimination (DcR3/PCT): $p < 0.01$/$p < 0.01$, AUC = 0.989/AUC = 0.981 (SP vs HC), $p < 0.01$/$p < 0.01$, AUC = 0.95/AUC = 0.74 (SP vs SIRS)	[125]
sFas, sepsis (SP)	Serum (SR) sFas levels in patients with SP were significantly higher than those in healthy controls (HC). SR sFas levels potentially work as a complementary tool for SP diagnosis.	P: 85 (SP) [54 m/31 f; (Md: 62)], C: 67 (HC) [44 m/23 f; (50)], sample numbers used for sFas assay: 67 (SP), 61 (HC)	SR (sFas, pg/ml), ELISA (Md, Rg): [SP (4437.26, 1092.68-22918.08)], [HC (3545.29, 1810.36-5414.05)]; $p < 0.01$ (SP vs HC)	[126]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
DcR3, sepsis (SP)	Serum (SR) DcR3 levels in patients with SP were significantly higher than those in healthy controls (HC). SR DcR3 levels may be a therapeutic target for SP treatment.	P: 36 (SP) [11 m/25 f; (Mn: 65.46, SD: 13.02)], C: 30 (HC) [10 m/20 f; (59.65, 11.04)]	SR (DcR3, ng/ml), ELISA (Mn, SD): [SP (1.44, 0.21)], [HC (0.22, 0.11)]; $p = 0.0029$ (SP vs HC)	[127]
DcR3, sepsis (SP) and systemic inflammatory response syndrome (SIRS)	Serum (SR) DcR3 levels in patients with SP were significantly higher than the levels in those with SIRS and healthy controls (HC). SR DcR3 levels were in good correlation with soluble urokinase-type plasminogen activator receptor (suPAR) and procalcitonin (PCT) levels. A combination of DcR3, suPAR, and PCT levels provided enhanced diagnostic values in distinguishing patients with SP from those with SIRS and HC, as compared to DcR3 alone.	SP: 34 (SP) [20 m/14 f; (Mn: 67.50, SD: 12.59)], 34 (SIRS) [20 m/14 f; (57.06, 21.91)], C: 20 (HC) [14 m/6 f; (63.20, 8.82)]	SR (DcR3, ng/ml), ELISA (Md, Rg): [SP (4.65, 0.38–27.62)], [SIRS (0.58, 0.00–8.72)], [HC (0.16, 0.00-0.73)]; $p < 0.001$ (SP vs HC), $p = 0.004$ (SP vs SIRS), $p = 0.016$ (SIRS vs HC), Corr. (vs DcR3): $p = 0.0022$, $r = 0.37$ (suPAR), $p = 0.0021$, $r = 0.37$ (PCT), ROC curve analysis for disease discrimination (DcR3 alone/DcR3, suPAR, and PCT combined): AUC = 0.990/AUC = 0.997, (95% CI: 0.971–1.000/0.989–1.000) (SP vs HC), AUC = 0.892/AUC = 0.933, (95% CI: 0.813–0.971/0.867–0.998) (SP vs SIRS)	[128]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
DcR3, sepsis (SP)	Postmortem serum (PM-SR) DcR3 levels in SP patients obtained via autopsy showed no statistically significant difference from those patients with carcinoma (CA) and non-SP-non-CA controls.	P: 19 (SP), 14 [culture-positive (CP)] [6 m/8 f; (Mn: 56.36, SD: 7.21)], 5 [culture-negative (CN)] [3 m/2 f; (73.00, 9.01)], C: 13 (CA) [9 m/4 f; (68.13, 8.45)], 15 (non-SP-non-CA) [10 m/5 f; (70.67, 14.96)], measurement time-point: autopsy	PM-SR (DcR3, ng/ml), ELISA (Mn, SD): [SP: CP (0.43, 0.25), CN (ca. 0.52, ca. 0.77)], [CA (0.53, ca. 0.57)], [non-SP-non-CA (ca. 0.21, ca. 0.16)]; $p = 0.63$ (among: SP-CP, SP-CN, CA, non-SP-non-CA), $p = 0.90$ (SP-CP vs CA)	[129]
DcR3, sepsis (SP) caused by bacteremia (BR) and systemic inflammatory response syndrome (SIRS)	Serum (SR) DcR3 levels in patients with SP were significantly higher than the levels in those with SIRS and healthy controls (HC). SR DcR3 levels were significantly higher in SP caused by Gram-negative bacteria (GN) than those in SP caused by Gram-positive bacteria (GP). SR DcR3 levels alone or in combination with C-reactive protein (CRP) was a promising biomarker for discriminating SP from patients with SIRS.	P: 15 (total SP) [8 m/7 f; (Mn: 50.87, SD: 17.80)], BR pathogens: 9 (GN), 6 (GP), 15 (SIRS) [6 m/9 f; (55.53, 14.13)], C: 15 (HC) [9 m/6 f; (48.40, 16.90)]	SR (DcR3, ng/ml), ELISA (Mn, SD): [total SP (5.21, 2.28)], [SIRS (1.96, 0.90)], [HC (0.95, 0.79)], [SP: GN (6.200, 2.2074), GP (3.733, 1.5384)]; $p < 0.001$ (overall: SP, SIRS, HC), $p < 0.05$ (SP vs SIRS, HC), $p = 0.034$ (SP: GN vs GP), ROC curve analysis for discriminating SP from SIRS: $p = 0.0001$, AUC = 0.920, (95% CI: 0.761–0.987) (DcR3 alone), $p = 0.0001$, AUC = 0.967 (95% CI: 0.828–0.999) (DcR3 and CRP combined)	[130]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Septic diseases caused by bacterial infections				
sFasL, necrotizing soft-tissue infections (NSTI)	PL sFasL levels in patients with NSTI caused by poly-microbial infections (type I) were significantly lower than the levels in those with NSTI caused by a single bacterial species (type II).	P: 251 (total NSTI) [138 m/113 f; (Mn: 59, SD: 15)], 117 (type I) [69 m/48 f; (59, 14)], 134 (type II) [69 m/ 65 f; (59, 15)], C: 20 (non-NSTI) [13 m/7 f; (46, 13)], 20 (SURG) [11 m/9 f; (59, 19)]	PL (sFasL, pg/ml), MPAA (Md): [total NSTI (ca. 20)], [non-NSTI (ca. 20)], [SURG (ca. 30)], heat map levels: [NSTI: type I (low); type II (high)]; $p = 0.005$ (NSTI: type I vs type II)	[131]
2. Non-septic diseases caused by viral infections				
sFas, chronic hepatitis C virus (CHC) and chronic hepatitis B virus (CHB) infection	Serum (SR) sFas levels in patients with CHC were significantly higher than those in healthy controls (HC), but were comparable to those in patients with CHB infection and autoimmune hepatitis (AH). SR sFas levels in patients with CHC exhibited a significant correlation with the histological severity of liver inflammation (HSLI), but no significant correlation with SR alanine aminotransferase (ALT) levels.	P: 68 (CHC) [56 m/12 f; (Mn: 46.9, SD: 10.4)], 15 (CHB) [10 m/5 f; (35.5, 14.0)], HSLI: 25 [minimal (MIN)], 27 [mild (MIL)], 14 [moderate (MOD)], 2 [severe (SEV)], C: 12 (AH) [1 m/11 f; (49.5, 15.2)], 17 (HC) [13 m/4 f; (36.9, 9.3)]	SR (sFas, ng/ml), ELISA (Mn, SD): [CHC (3.24, 1.55)], [HC (1.70, 1.01)], [CHB (3.71, 1.36)], [AH (2.74, 0.95)]; [CHC: MIN (ca. 2.6, ca. 1.1), MIL (ca. 3.1, ca. 1.8), MOD/SEV (ca. 3.8, ca. 1.6)]; $p < 0.01$ (CHC, CHB vs HC), $p < 0.05$ (AH vs HC), p = ns (CHC vs CHB, AH; CHB vs AH), Corr. (vs sFas): $p < 0.01$, $r_s = 0.37$ (HSLI), $p = 0.30$, $r_s = 0.13$ (ALT)	[132]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Non-septic diseases caused by viral infections				
sFas and sFasL, chronic hepatitis C virus (CHC) infection	Plasma (PL) sFas levels in patients with CHC infection were higher than the levels in those with HIV-1 infection (HIV-1) and healthy controls (HC). No statistically significant difference in PL sFasL levels was observed among the CHC, HIV-1, and HC groups. PL sFas levels in patients with CHC showed significant positive correlations to PL alanine aminotransferase (ALT) and tumor necrosis factor (TNF)-α levels.	P: 17 (CHC) [10 m/7 f; (Mn: 47.52, SD: 12.46)], C: 19 (HIV-1) (nd/nd, nd), 10 (HC) (nd/nd, nd)	PL (sFas/sFasL, ng/ml), ELISA (Mn, SD): sFas: [CHC (2.69, 2.86)], [HIV-1 (0.809, 1.806)], [HC (0.0035, 0.011)]; sFas: $p = 0.008$ (CHC vs HIV-1), $p = 0.99$ [CHC vs HC (but, undetectable in 9/10 of HC)], sFasL: $p = 0.09$ (overall: CHC, HIV-1, HC), Corr. (vs sFas in CHC): $p < 0.000$, $r = 0.78795$ (ALT), $p < 0.000$, $r = 0.891$ (TNF-α)	[133]
sFasL, hepatitis virus-C related liver cirrhosis (HCV-LC)	Blood (BL) sFasL levels in patients with HCV-LC did not show a statistically significant difference between those from the hepatic vein (HV) and those from the peripheral vein (PV). A strong correlation was observed for BL sFasL levels between HV and PV.	P: 15 (HCV-LC) [9 m/6 f; (Mn: 58, Rg: 39–74)]	BL (from HV and PV in the same session) (sFasL, ng/ml), ELISA (DDA) (Md, SD): [HCV-LC: HV (0.87, 0.76), PV (0.81, 0.61)]; Corr. (sFasL): $p < 0.01$, $r = 0.634$ (HV vs PV)	[134]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Non-septic diseases caused by viral infections				
DcR3, Chronic hepatitis-B virus infection (CHB)	Serum (SR) DcR3 levels in patients with active CHB and negative hepatitis B-virus (HBV) antigen (CHB-ACT) were significantly higher than the levels in those with inactive CHB carrying hepatitis B surface antigen (CHB-INACT) and healthy controls (HC). SR DcR3 levels in patients with CHB-ACT were correlated with HBV-DNA and alanine aminotransferase (ALT) levels. SR DcR3 levels may detect patients with CHB-ACT requiring medical treatment.	P: 80 (total CHB), 48 (ACT) [31 m/17 f; (Mn: 35.6, SD: 12.3)], 32 (INACT) [20 m/12 f; (34.7, 14.1)], C: 96 (HC) (nd/nd, nd)	SR (DcR3, ng/ml), ELISA (Mn, SD): [CHB: ACT (1.92, 0.68), INACT (0.95, 0.26)], [HC (0.80, 0.25)]; $p < 0.0001$ (CHB-ACT vs CHB-INACT, HC), $p = 0.014$ (CHB-INACT vs HC), Corr. (vs DcR3 in CHB-ACT): $p < 0.0001$, $r = 0.819$ (HBV-DNA), $p < 0.0001$, $r = 0.704$ (ALT)	[135]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Non-septic diseases caused by viral infections				
DcR3, hemorrhagic fever with renal syndrome (HFRS) caused by Hantaan virus infection	Serum (SR) DcR3 levels in HFRS patients at any clinical stage and disease phases were higher than those in healthy controls (HC). SR DcR3 levels increased initially from the febrile phase, reached peak value during the oliguric phase, and then decreased gradually until the convalescent phase in all HFRS patients with any severity. SR DcR3 levels in patients with HFRS during the convalescent phase were significantly higher than those in HC, with the highest levels in the critical group.	P: 106 (total HFRS) (nd/nd; nd), 27 [mild group (MIL)], 27 [moderate group (MOD)], 30 [severe group (SEV)], 22 [critical group (CRI)], C: 20 (HC) (nd/nd, nd), measurement time-points: febrile phase (FE), hypotensive phase (HY), oliguric phase (OL), polyuric phase (PO), convalescent phase (CO) (for HFRS patients), baseline (BS) (for HC)	SR (DcR3, pg/ml), ELISA (Mn): [HFRS-MIL: FE (ca. 78), HY (ca. 90), OL (ca. 100), PO (ca. 66), CO (ca. 53)], [HFRS-MOD: FE (ca. 100), HY (ca. 110), OL (ca. 120), PO (ca. 73), CO (ca. 62)], [HFRS-SEV: FE (ca. 120), HY (ca. 140), OL (ca. 150), PO (ca. 90), CO (ca. 77)], [HFRS-CRI: FE (ca. 130), HY (ca. 160), OL (ca. 180), PO (ca. 100), CO (ca. 100)], [HC-BS (ca. 32)]; $p < 0.01$ (HFRS: any disease severity, at any clinical phase vs HC-BS)	[136]
DcR3, human immunodeficiency virus-1 (HIV1) infection	Serum (SR) DcR3 levels of total patients with HIV1-infection (HIV1) were significantly higher than those in healthy controls (HC). SR DcR3 levels in patients infected with subtype-B were significantly higher than those in patients with subtype-CRF01_AE. SR DcR3 levels in patients with HIV1 with slow disease progression speed (DPS) were significantly higher than those in patients with fast and typical DPS.	P: 61 (total HIV1) [50 m/11 f; (Md: 32, SEM: 1.3, Rg: 19–60), 43 [subtype B (B); 18 [subtype CRF01_AE (CRF)], DPS: 23 [fast (FA)], 25 [typical (TY)], 13 [slow (SL)], measurement time-points: 1, 2, 3, 4, 5, 6, >6 years (Y) after diagnosis, C: 145 (HC) [100 m/45 f; (36, 0.5, 22–51)]	SR (DcR3, ng/ml), ELISA (Md, Rg): [total HIV1 (0, 0–226)], [HC (majority did not have detectable level)], [HIV1: B (2, 0–226), CRF (0, 0–65.1)]; $p < 0.001$ (total HIV1 vs HC; HIV1: B vs CRF), $p = 0.02$ (6Y), $p = 0.003$ (> 6Y) (DPS: SL vs FA and TY)	[137]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Non-septic diseases caused by viral infections				
sFas and sFasL, human immunodeficiency virus-1 (HIV1) infection (adult)	A decrease in plasma (PL) sFasL, but not sFas, levels were significantly correlated with a change in HIV1 viral load (HIV1-VL) six months after antiretroviral therapy (ART). High PL sFasL levels indicated high HIV1-VL. sFasL levels could be a better and more affordable alternative biomarker of diseases caused by HIV1 virus infection in adults.	P: 60 (total HIV1) [38 m/22 f; (Mn: 34.3, SD: 7.8)], measurement time-points: baseline (BS) and 6 months (6M) after ART, 20 [<1 log change in HIV1-VL after 6M (6M-SC)], 40 [>1 log change in HIV1-VL after 6M (6M-LC)]	PL (sFas/sFasL, pg/ml), ELISA (Mn, Rg): [HIV1: BS (nd/153.7, 95–300/51–321), 6M (nd/88.1, 80–290/27–231)], change (Δ) in sFasL (Mn): [HIV1-6M: SC (−5.4), LC (−87.2)]; p = 0.06 (Δ in 6M-SC vs Δ in 6M-LC), Corr.: p = 0.03, r = 0.49 (Δ in HIV1-VL after 6M vs Δ in sFasL level after 6M)	[138]
sFas and sFasL, human immunodeficiency virus-1 (HIV1) infection (pediatric)	Plasma (PL) sFasL, but not sFas, levels showed a significant correlation with viral loads in pediatric patients infected with HIV1 (HIV1-VL), but not with CD4+ cell parameters. Measurements of PL sFasL levels could monitor pediatric HIV1 disease progression in developing countries.	P: 22 (HIV1) [9 m/13 f; (Rg: 0.75–7)],	PL (sFas/sFasL, pg/ml), ELISA (Md, Rg): (1517.5/126, 987–3217/36–299); Corr. (vs sFas/sFasL): p = 0.60/p = 0.01, r = 0.12/r = 0.56 (HIV1-VL), p = 0.18/p = 0.18, r = −0.30/r = −0.29 (CD4+ cell counts), p = 0.19/p = 0.18, r = −0.29/r = −0.30 (CD4+ cell %)	[139]
sFas and sFasL, Ebola virus disease (EVD) caused by Ebola virus infection	Serum (SR) sFasL levels in patients with moderate (MOD) EVD were significantly higher than those in healthy controls (HC), while most EVD patients had SR sFas levels that fell within the HC reference value.	P: 7 (total EVD), 5 (MOD), 2 (severe) [5 m/2 f; (Rg: 29–59)], C: 10 (HC) (nd/nd; nd)	SR (sFas/sFasL, log pg/ml), MPAA (raw data): [1 (sFas)/6 (sFasL) in 7 EVD patients had higher measurement values than each reference value range obtained from HC]; sFasL: p = 0.0154270 (EVD-MOD vs HC)	[140]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Non-septic diseases caused by viral infections				
sFasL, acute hepatitis A (AHA) and acute hepatitis B (AHB) caused by hepatitis-A virus and hepatitis-B virus infection	Serum (SR) sFasL levels in patients with AHA, but not with AHB, were significantly higher than those in healthy controls (HC). A significant correlation was observed between SR sFasL and SR alanine aminotransferase (ALT) levels in patients with AHB, but not with AHA.	P: 46 (AHA) [26 m/ 20 f; (Md: 33.6, Rg: 22–49)], 16 (AHB) [13 m/3 f; (35.8, 19–67)], C: 14 (HC) [12 m/2 f; (32.1, 24–44)]	SR (sFasL, ng/l), ELISA (Mn): [AHA (ca. 58)], [AHB (ca. 42)], [HC (ca. 26)]; $p < 0.001$ (AHA vs HC), p = ns (AHB vs HC) Corr. (sFasL vs ALT): $p < 0.05$, $r = 0.60$ (AHB), p = ns, $r = 0.14$ (AHA)	[141]
DcR3, chronic hepatitis-B (CHB) with liver fibrosis (LF)	Serum (SR) DcR3 levels in CHB patients were significantly higher than those in healthy controls (HC). Patients with active CHB (CHB-ACT) had significantly higher SR DcR3 levels compared with those of CHB carriers (CHB-CAR). Higher SR DcR3 levels were associated to patients with more complicated liver fibrosis (LF). SR DcR3 levels may serve as a novel CHB disease activity and LF grade diagnosis indicator.	P: 128 (total CHB) [72 m/56 f; (Md: 38, Rg: 20–65)], 61 (ACT: HBV DNA > 10^5 copies/ml and ALT >40 IU/l), 67 (CAR), LF grade: 45 (S0: no LF) (20 m/15 f), 74 (S1-3: gradual increase in LF degree) (41 m/33 f), 9 (S4: liver cirrhosis) (6 m/3 f), C: 60 (HC) [36 m/24 f; (35, 21–63)]	SR (DcR3, ng/ml), ELISA (Mn, SD): [total CHB (213.01, 14.50)], [HC (0.24, 0.06)], [CHB: ACT (253.82, 32.12), CAR (151.35, 12.03); S0 (109.66, 16.08), S1-3 (227.37, 18.71), S4 (355.26, 50.24)]; $p < 0.001$ (total CHB vs HC), $p = 0.0224$ (CHB: ACT vs CAR), $p < 0.001$ (CHB: S0 vs S1-3, S4; S1-3 vs HC), $p = 0.013$ (CHB: S1-3 vs S4)	[142]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Non-septic diseases caused by viral infections				
sFasL, viral myocarditis (VMC) caused by enterovirus and adenovirus infection (pediatric)	Serum (SR) sFasL levels in patients with pediatric VMC treated with *Astragalus mongholicus (Fisch.) Bge* (AB) were significantly lower than patients treated with placebo (PL). SR sFasL levels in patients with VMC were significantly correlated with the expression levels of immune-regulatory microRNAs (miR), miR-146b, and miR-155.	P: 68 (total VMC), 34 [AB treatment (AB)] [18 m/16 f; (Rg: 5.2–11.3)], 34 [PL treatment (PL)] [17 m/17 f; (5.3–11.7)]	SR (sFasL, pg/ml), ELISA (Mn, SD): [VMC: AB (25.59, 3.12), PL (78.31, 9.02)]; $p < 0.05$ (AB vs PL), Corr. (vs sFasL): $p = 0.001$, $r_s = 0.61$ (miR-146b), $p = 0.001$, $r_s = 0.64$ (miR-155)	[143]
sFas and sFasL, human immune-deficiency virus-1 (HIV1) infection (pediatric)	Plasma (PL) sFas and sFasL levels in patients with pediatric HIV1-infection (HIV1) were significantly higher than those in total HIV1-uninfected children (non-HIV1). However, PL sFas and PL sFasL levels in patients infected with HIV1 did not show significant differences from those in healthy controls (HC) and HIV1-exposed uninfected subjects (HEU), respectively. PL sFasL, but not sFas, levels in antiretroviral treatment (ART)-naïve patients were significantly correlated with CD4-positive cell count (% CD4+).	Total: 212 [100 m/112 f; (nd)], P: 88 (total HIV1) [nd/nd (Mn: 6.70, SD: 3.23, Rg: 1–15)], 44 [ART-naïve (ART-N)], 44 [ART-received (ART-R)], C: 124 (total non-HIV1), 86 (HEU) [nd/nd (5.53, 2.01, 0.75–13)], 38 (HC) [nd/nd (7, 2.24, 1–15)]	PL (sFas/sFasL, pg/ml), ELISA (Md, Iqr): [total HIV1 (657.7/136.5, 365.28/91.68)], [total non-HIV1 (289/120.6, 314.81/84.40)]; $p < 0.0001$/$p = 0.009$ (total HIV1 vs total non-HIV1), $p = 0.0001$/p = ns (total HIV1 vs non-HIV1-HEU), p = ns/$p = 0.001$ (total HIV1 vs HC), $p = 0.0001$/$p = 0.01$ (non-HIV1: HEU vs HC), Corr. (sFas/sFasL vs % CD4+): $p = 0.93$/$p = 0.04$, $r_s = -0.01$/$r_s = -0.31$ (HIV1-ART-N), $p = 0.2$/$p = 0.05$, $r_s = 0.2$/$r_s = 0.3$ (HIV1-ART-R)	[144]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Non-septic diseases caused by viral infections				
DcR3, chronic hepatitis-B (CHB) caused by hepatitis-B virus (HBV) infection	Serum (SR) DcR3 levels in CHB patients were significantly higher than those in healthy controls (HC), while patients with active CHB (CHB-ACT) had higher DcR3 levels than CHB carrier (CHB-CAR). SR DcR3 levels in CHB patients significantly correlated with HBV-DNA copy number and liver injury parameters, including SR alanine aminotransferase (ALT), and SR aspartate aminotransferase (AST).	P: 132 (total CHB) [74 m/58 f; (Md: 38, Rg: 21–66)], nd (ACT), nd (CAR), C: 70 (HC) [41 m/29 f; (35, 20–63)]	SR (DcR3, ng/ml), ELISA (Mn): [total CHB (ca. 4.0)], [HC (ca. 1.0)], [CHB: ACT (ca. 4.4), CAR (ca. 2.8)]; $p < 0.01$ (total CHB vs HC; CHB: ACT vs CAR), Corr. (vs DcR3): $p < 0.001$, $r = 0.5733$ (HBV-DNA), $p = 0.0001$, $r = 0.3670$ (ALT), $p < 0.0001$, $r = 0.3844$ (AST)	[145]
sFas and sFasL, hepatitis-B virus (HBV) infection [mono-infection and co-infection with human immune-deficiency virus (HIV)]	Serum (SR) sFas and sFasL levels in patients with HBV mono-infection (HBV-MO) were significantly higher than those in healthy controls (HC). Co-infection with HIV further elevated SR sFas levels, whereas SR sFasL levels of HBV/HIV co-infected patients (HBV-COHIV) were much lower than those in HBV-MO. In HBV-MO, a significant correlation between SR sFas and programmed death (PD)-L1 levels and that between SR sFasL and PD-1 levels were observed.	P: 45 (total HBV), 30 (MO) [nd/nd; (Mn: 41.1, SD: 14.95, Md: 35, Iqr: 27.5)], 15 (COHIV) [nd/nd; (45.1, 7.9, 45, 40)], C: 20 (HC) [nd/nd; (26.9, 6.1, 26, 22)]	SR (sFas/sFasL, pg/ml), MPAA (Mn, SD): [HBV: MO (10129.1/73.2, 3511.4/29.1), COHIV (18384.1/7.0, 9775.4/10.9)], [HC (7114.2/9.2, 2682.4/76.7)]; $p < 0.0001$/$p < 0.0001$ (HBV-MO vs HC), $p < 0.0001$/$p = 0.3412$ (HBV-COHIV vs HC), Corr. (HBV-MO): $p < 0.01$, $r = 0.48$ (PD-L1 vs sFas), $p < 0.05$, $r = 0.46$ (PD-1 vs sFasL):	[146]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Non-septic diseases caused by viral infections				
sFas, liver fibrosis (LF), chronic hepatitis (CH) caused by hepatitis-B virus (HBV) and hepatitis-C virus (HCV) infection (pediatric)	Serum (SR) sFas levels in patients with hepatitis-B virus (HBV) or chronic hepatitis-C virus (HCV) possessing portal LF with few septa (F2)/numerous LF without cirrhosis (F3) were significantly lower than those in patients with no LF (F0)/portal LF without septa (F1). A combination of SR sFas levels with aspartate transaminase to platelet ratio index (APRI) and monocyte chemoattractant protein-1 (MCP-1) level could differentiate LF stage F2/F3 from F0/F1 in pediatric CH caused by HBV or HCV infection.	P: 16 (total CH) [6 m/10 f; (Md: 12.6, Rg: 3.4–17.9)], 6 (F0/F1) [3 m/3 f; (13.0, 4.4–17.1)], 10 (F2/F3)] [3 m/7 f; (8.9, 3.4–17.9)], measurement time-points (SR sFas level, n = 14): [5 0–4 years old (0–4 YO), 1 (5-9 YO), 8 (≥ 10 YO)]	SR (sFas, nd), nd (Md, Rg): [total CH (6.1, 3.3–7.9)], [CH: F0/F1 (6.9, 4.9–7.9), F2/F3 (5.6, 3.3–6.3); 0–4 YO (4.9, 3.3–7.5), 5–9 YO (6.0, 6.0-6.0), ≥ 10 YO (6.2, 5.0–7.9)]; p = 0.046 (CH: F0/F1 vs F2/F3), p = 0.11 (among CH: 0–4 YO, 5–9 YO, ≥ 10 YO), ROC curve analysis for prediction of CH-F2/F3: p = nd, AUC = 0.82 (95% CI: 0.57–1.00) (sFas alone), p < 0.001, AUC = 0.92 (95% CI: 0.75–1.00) (APRI x MCP-1/sFas)	[147]
sFasL, severe acute respiratory syndrome coronavirus disease 2019 infection (COVID-19)	Serum (SR) or plasma (PL) sFasL levels in patients who died of COVID-19 were significantly lower than those in healthy controls (HC). SR/PL sFasL levels decreased in a stepwise manner associated with the disease progression from moderate to critical.	P: 175 (total COVID-19) [132 m/43 f; (Md: 60, Iqr: 51–69)], disease severity grade: 122 [critical (CR)], 23 [severe (SE)], 30 [mild/moderate (MO)], 33 [deceased (DE)], 142 (survived), C: 43 (HC) [24 m/19 f; (Mn: 44.9, Rg: 25.2–71)]	SR or PL (sFasL, pg/ml), MPAA (Md, Iqr): [COVID-19: DE (16.71, 10.30–18.26), CR (17.72, 12.30–25.28), SE (21.24, 13.30–26.23), MO (35.19, 23.93–41.32)], [HC (38.41, 28.76–52.30)]; p < 0.0001 (COVID-19: DE, CR, SE vs HC), p < 0.001 (COVID-19: DE, CR vs MO), p < 0.05 (COVID-19: SE vs MO)	[148]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Non-septic diseases caused by viral infections				
sFas and sFasL, acute hepatitis-B (AHB) and chronic hepatitis-B (CHB) caused by hepatitis-B virus (HBV) infection	Serum (SR) sFas and sFasL levels in patients with AHB and CHB were significantly higher than those in healthy controls (HC). SR sFas and sFasL levels exhibited significant negative correlations with the immunomodulatory protein soluble fibrinogen-like protein 2 (sFGL2) levels in SR.	P: 20 (AHB) [11 m/9 f; (Mn: 44, SD: 6.8, Rg: 31–57)], 55 (CHB) [33 m/22 f; (47, 9.2, 20–62)], C: 15 (HC) [8 m/7 f; (47, 10.5, 25–65)]	SR (sFas/sFasL, ng/ml), ELISA (Mn, SD) [AHB (ca. 3.0/ca. 1.6, ca. 0.59/ca. 0.20)], [CHB (ca. 4.0/ca. 2.2, ca. 0.75/ca. 0.46)], [HC (ca. 1.8/ca. 0.98, ca. 0.26/ca. 0.37)]; $p \leq 0.001$/$p \leq 0.001$ (AHB vs CHB, HC; CHB vs HC), Corr. (vs sFas/sFasL): $p < 0.0001$/$p < 0.0001$, $r^2 = 0.29$/$r^2 = 0.25$ (sFGL2)	[149]
sFasL, cytokine storm syndrome (CSS) caused by the novel coronavirus SARS-Cov-2 infection (COVID-19)	Serum (SR) sFasL levels in patients with COVID-19 were significantly lower than the levels in those with secondary hemophagocytic lympho-histiocytosis (sHLH) or macrophage activation syndrome (MAS). SR sFasL levels in patients with COVID-19 decreased with higher disease severity. SR sFasL levels clearly discriminated COVID-19 from other well-recognized diseases with CSS.	P: 30 (COVID-19) [28 m/2 f; (Md: 57, Rg: 30–81)], disease severity: 17 [critical (CR)] [16 m/1 f; (60, 49–76)], 6 [severe (SE)] [all m; (53, 49–73)], 7 [moderate (MO)] [6 m/1 f; (54, 30–81)], C: 22 (sHLH) [14 m/8 f; (53.5, 1.5–86.5)], 28 (MAS) [10 m/18 f; (44.0, 8.0–66.0)], 9 (HC) [4 m/5 f; (28, 7–55)]	SR (sFasL, pg/ml), MPAA (Md): [COVID-19: CR (ca. 6.0), SE (ca. 6.3), MO (ca. 16)], [sHLH (ca. 27)], [MAS (ca. 16)], [HC (ca. 17)]; $p < 0.0001$ (COVID-19-CR vs sHLH), $p < 0.05$ (COVID-19-SE vs sHLH), $p < 0.001$ (COVID-19-CR vs MAS), $p < 0.01$ (COVID-19-CR vs HC)	[150]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Other non-septic diseases				
sFas and sFasL, cerebral malaria (CM) caused by *Plasmodium falciparum* infection	Post-mortem serum (PM-SR) sFas and sFasL levels did not show statistically significant differences among patients with CM or severe malarial anemia (SMA), and non-malaria death (NM) controls. Post-mortem cerebrospinal fluid (PM-CSF) sFasL, but not sFas, levels were significantly higher in CM patients than those in NM controls.	P: 14 (total malaria death), 9 (CM) [4 m/5 f; (Mn: 61.2, SD: 3.1)], 5 (SMA) [3 m/2 f; (14.6, 1.2)], C: 5 (NM) [3 m/2 f (79.0, 4.3)]	PM-SR and PM-CSF (sFas/sFasL, pg/ml), ELISA (Md): [CM: PM-SR (ca. 9300/ca. 310), PM-CSF (ca. 92/ca. 4.8)], [SMA: PM-SR (ca. 9300/ca. 470), PM-CSF (ca. 70/ca. 4.2)], [NM: PM-SR (ca. 10000/ca. 280), PM-CSF (ca. 43/ca. 1.6)]; p = ns/p = ns (PM-SR: CM vs SMA, NM; PM-CSF: SMA vs NM), p = ns/p = 0.002 (PM-CSF: CM vs NM)	[151]
sFas and sFasL, cerebral malaria (CM) caused by *Plasmodium falciparum* infection	Plasma (PL) sFas and sFasL levels increased with disease severity in CM, however only PL sFas levels in non-survivors (non-SUV) showed significant differences from those in all other disease groups, including CM survivors (SUV), mild malaria (<25000 parasites/μl blood) (MM), and healthy controls (HC). PL sFasL levels in HC were significantly different from those in the other groups. PL sFas levels may be a potential biomarker of CM severity and mortality.	P: 60 (total CM), 12 (non-SUV) [6 m/6 f; (Mn: 20, SD: 16)], 48 (SUV) [34 m/14 f; (25, 19)], 48 (MM) [28 m/20 f; (19, 14)], C: 25 (HC) [18 m/7 f; (22, 14)]	PL (sFas/sFasL, log pg/ml), ELISA (Md): [CM: non-SUV (ca. 4.1/ ca. 2.9), SUV (ca. 3.9/ca. 2.5)], [MM (ca. 3.7/ca. 2.5)], [HC (ca. 3.6/ca. 2.2)]; p < 0.0001/p = 0.0174 (overall: total CM, MM, HC), p < 0.05/p = ns (CM: non-SUV vs SUV), p < 0.0045/p = ns (CM-non-SUV vs MM), p < 0.0045/p < 0.05 (CM-non-SUV vs HC), p < 0.05/p = ns (CM-SUV vs MM), p < 0.05/p < 0.05 (CM-SUV vs HC), p = ns/p < 0.05 (MM vs HC)	[152]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Other non-septic diseases				
sFasL, tuberculous pleurisy (TBP) caused by *Mycobacterium tuberculosis* infection	Pleural effusion (PE) sFasL levels in patients with TBP were significantly higher than those in non-TBP controls. PE sFasL levels in patients with TBP showed a significant difference from those in all non-TBP subgroups. PE sFasL levels were efficient TBP diagnosis tools with comparable accuracy to adenosine deaminase (ADA) and interferon (IFN)-γ. The above features made PE sFasL levels a potentially better biomarker for TBP diagnosis at early stages.	P: 23 (TBP) [17 m/6 f; (Md: 76.0, Iqr: 68.0–82.0)], C: 56 (total non-TBP) [31 m/25 f; (76.0, 66.3–81.8)], 7 [bacterial parapneumonic effusion/empyema (BPE)], 22 [malignancy (MG)], 23 [transudate (TU)], 4 [miscellaneous (MC)]	PE (sFasL, pg/ml), ELISA (Md, Iqr): [TBP (57.3, 42.1–84.9)], [total non-TBP (27.4, 23.1–37.9)], [non-TBP: BPE (38.0, 29.6–50.4), MG (30.2, 23.1–44.8), TU (24.5, 23.1–28.0), MC (23.8, 17.7–36.9)]; $p < 0.001$ (TBP vs non-TBP: total, MG, TU), $p = 0.039$ (TBP vs non-TBP-BPE), $p = 0.003$ (TBP vs non-TBP-MC), ROC curve analysis for diagnosing TBP: AUC = 0.879 ± 0.046 (sFasL), AUC = 0.914 ± 0.033 (ADA), 0.911 ± 0.042 (IFN-γ)	[153]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Other non-septic diseases				
DcR3, tuberculosis (TB) caused by *Mycobacterium tuberculosis* infection	Baseline serum (SR) DcR3 levels in patients with active TB (TB-ACT) were significantly higher than those in latent TB infection contacts (TB-LAT) and non-infected controls (non-TB). SR DcR3 levels in patients with TB did not significantly change after a one-month anti-TB treatment. SR DcR3 levels among TB-ACT non-survivors (non-SUV) were higher, but not statistically significant, as compared with those in TB-ACT survivors (SUV). High DcR3 levels may be a highly sensitive criterion for identifying active TB cases from interferon-release assay (IGRA)-positive TB-LAT contacts and for poorer prognosis in patients with TB.	P: 100 (total TB-ACT), [62 m/38 f; (Mn: 70.3, SD: 16.2)], 79 (SUV) [48 m/31 f; (68.2, 16.9)], 21 (non-SUV) [14 m/7 f; (78.3, 9.6)], measurement time-points: at diagnosis (BS), after anti-TB treatment for 1 month (1M, n = 55), 91 (TB-LAT: IGRA-positive contacts) [33 m/58 f; (51.3, 15.6)], C: 92 (non-TB: IGRA-negative contacts) [32 m/60 f; (44.6, 16.9)]	SR (DcR3, ng/ml), ELISA (Mn, SD): [TB-ACT: BS (3.97, 4.0), 1M (4.59, 3.2); SUV (3.6, 3.8), non-SUV (5.3, 3.7)], [TB-LAT (0.64, 0.6)], [non-TB (1.21, 3.0)]; $p < 0.001$ (TB: ACT-BS vs LAT), $p = 0.286$ (TB-ACT: BS vs 1M), $p = 0.078$ (TB-ACT: SUV vs non-SUV), $p = 0.082$ (TB-LAT vs non-TB), risk analysis for TB-ACT (DcR3, per 1 ng/ml increment): $p < 0.001$, OR = 11.91 (95% CI: 4.03–35.17), ROC curve analysis for TB diagnosis: $p < 0.001$, AUC = 0.932, log-rank test for cumulated survival: $p = 0.004$ (DcR3 in ng/ml: >2.67 vs ≤2.67)	[154]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Other non-septic diseases				
sFasL, leptospirosis (LS) caused by *Leptospira interrogans* infection (severe)	Serum (SR) sFasL levels in non-survivor patients (non-SUV) with severe LS (SLS) were significantly higher than those in survived patients (SUV) and healthy controls (HC). Increased SR sFasL levels at the time of hospital admission were strongly associated with higher mortality in patients with LS.	P: 52 (total SLS) [37 m/15 f; (Md: 45, Iqr: 33–55)], 14 (non-SUV), 38 (SUV), C: 20 (HC) (nd/nd, nd), measurement time-point: at hospital admission	SR (log10 sFasL, ng/ml), ELISA (Mn, SD): [SLS: non-SUV (2.7, 0.4), SUV (1.9, 0.5)], [HC (1.8, 0.3)]; $p < 0.01$ (SLS- non-SUV vs SLS-SUV, HC)	[155]
sFasL and DcR3, tuberculosis pleural effusion (TPE) caused by *Mycobacterium tuberculosis* infection	Pleural effusion (PE) sFasL and DcR3 levels in patients with tuberculous pleural effusion (TPE) were significantly higher than in those with malignant PE (MPE) and other PE (OPE). PE DcR3 levels were an independent factor associated with TPE. The combination of PE DcR3 levels with interferon (IFN)-γ, adenosine deaminase (ADA), and soluble tumor necrosis factor receptor (sTNF-R)1 levels may significantly improve diagnostic efficacy, such as sensitivity (SE) and specificity (SP), for TPE compared with the conventional method using IFN-γ or ADA alone.	P: 35 (TPE) [26 m/9 f; (Mn: 66.5, SD: 18.9)], C: 60 (total non-TPE) [38 m/22 f; (67.0, 14.3)], 46 (MPE) [27 m/19 f; (67.3, 14.6)], 14 (OPE) [11 m/3 f; (65.8, 13.6)]	PE (sFasL/DcR3, pg/ml), MPAA (sFasL) and ELISA (DcR3) (Mn, SD): [TPE (49.2/16943, 185.1/11610)], [total non-TPE (4.1/8720, 17.8/4896)], [non-TPE: MPE (4.3/8959, 19.5/5485), OPE (3.3/7950, 11.3/2065)]; $p < 0.05$/$p < 0.05$ (TPE vs non-TPE-MPE), p = ns/$p < 0.05$ (TPE vs non-TPE: total, OPE), risk analysis for TPE (DcR3 in ng/ml: ≥9.3 vs <9.3): p = 0.026, OR = 4.75 (95% CI: 1.20–18.77), ROC curve analysis for TPE diagnosis (SE/SP): 82.9 %/86.7 % (DcR3, IFN-γ, ADA, and sTNF-R1 combined), 65.7 %/96.7 % (IFN-γ alone), 40.0 %/98.3 % (ADA alone)	[156]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Other non-septic diseases				
sFasL, tuberculous pleurisy (TBP) caused by *Mycobacterium tuberculosis* infection	Pleural effusion (PE) sFasL levels in patients with TBP (TPE) were significantly higher than those in patients with malignant pleural effusion (MPE) or parapneumonic effusion/pleural effusion (PPE/PE). The risk of TPE was significantly elevated with increasing PE sFasL level, and the diagnostic efficacy of PE sFasL level for TPE was not virtually affected by age.	P: 222 (total PE) [130 m/92 f; (Md: 64.5, Iqr: 54–77)], 60 (TPE) (53.5, 35.0–71.5), 90 (MPE) (69.0, 60.0–76.0), 35 (PPE/PE) (60.0, 50.0–71.0), 30 [transudates (TU)] (78.0, 58.0–83.0), 7 [other PE (OPE)] (61.0, 51.0–72.0)	PE (sFasL, pg/ml), ELISA (Md, Iqr): [total PE (40.9, 18.9–79.9)], [TPE (86.0, 64.1–133.2)], [MPE (19.6, 13.7–31.9)], [PPE/PE (22.3, 16.2–32.2)], [TU (nd, nd)], [OPE (nd, nd)]; $p < 0.0001$ (among TPE, MPE, PPE/PE), risk analysis for TPE (sFasL): $p < 0.0001$, OR = 1.06 (95% CI: 1.03–1.09), ROC curve analysis for TPE diagnosis (sFasL): AUC = [0.933 (age ≥45), 0.918 (age ≤55), 0.939 (age >55)]	[157]
sFasL, malaria (MA) caused by *Plasmodium falciparum* infection and bacteremia (BR)	Serum (SR) sFasL levels in patients with MA were substantially higher than those in patients with BR and healthy controls (HC). SR sFasL levels were one of the best disease predictors with good accuracy, which may contribute to the development of innovative point-of-care tests to guide treatment decisions in MA-endemic regions.	P: 38 (MA) [16 m/22 f; (Md: 24.0, Iqr: 13.5–37.5)], 30 (BR) [15 m/15 f; (28.5, 12.0–36.0)], C: 10 (HC) [7 m/3 f; (20, 13.5–36)]	SR (sFasL, ng/ml), MPAA (Md, Iqr): [MA (ca. 0.042, ca. 0.030–ca. 0.060)], [BR (ca. 0.018, ca. 0.013–ca. 0.020)], [HC (ca. 0.025, ca. 0.015–ca. 0.029)]; prediction power for MA diagnosis (sFasL): 82 % (prediction accuracy), (95 % CI: 62–94%)	[158]

3.3.2. Non-septic diseases caused by viral infections [132–150]

Another area relevant to the infectious disease section in this survey was non-septic diseases caused by viral infections. Diseases caused by acute or chronic hepatitis virus infection are the most frequently investigated disorders. In cases of acute hepatitis virus infection, the mean SR sFas and sFasL levels in patients with acute hepatitis A and B were higher than those in healthy controls; however, the statistical difference depended on the study [141,149]. A significant correlation was observed between SR sFasL and alanine aminotransferase (ALT) levels for acute hepatitis B alone [141]. SR DcR3 levels in patients with chronic hepatitis B virus (HBV) infection were consistently higher than those in healthy controls, and DcR3 levels in patients with active disease were significantly higher than those in inactive HBV carrier [135,142,145]. Higher SR DcR3 levels are associated with a more complicated degree of liver fibrosis (LF) [142]. DcR3 levels were significantly correlated with SR HBV-DNA copy numbers, ALT levels, and aspartate transaminase levels in patients infected with HBV [135,145]. SR sFas and SR sFasL levels in HBV-infected patients behaved oppositely when co-infected with human immunodeficiency virus (HIV). The former further increased while the latter markedly decreased compared with those in patients mono-infected with HBV [146]. In patients infected with chronic hepatitis C virus (HCV), PL sFas, but not sFasL levels, were significantly higher than those in healthy controls and HIV-infected patients [133]. SR/PL sFas levels in adult patients with chronic hepatitis-C exhibited a significant positive correlation with the histological severity of liver inflammation [132], hepatocellular injury marker, ALT level, and inflammation marker, TNF-α level [133]. In contrast, in pediatric patients suffering from chronic B or C hepatitis, SR sFas levels in patients with portal LF with few septa or those possessing numerous septa without CIR were significantly lower than those in patients with no LF or those with portal LF without septa [147].

In patients infected with the HIV-1 virus, SR DcR3 levels were significantly elevated compared to those in healthy controls [137]. A significant difference in DcR3 levels was observed between patients infected with HIV-1 subtype-B strain and those infected with subtype CRF01_AE strain. Positive strong correlations between PL sFasL levels and HIV-1 viral loads have been identified in both adult [138] and pediatric [139] patients receiving antiretroviral therapies. However, the statistical significance of the correlation with CD4-positive cell percentage in pediatric patients depended on the study [139,144]. Recently, SR/PL sFasL levels in patients with severe acute respiratory syndrome (SARS-CoV-2) causing the coronavirus 2 (COVID-19) infection have been published. SR sFasL levels in patients with COVID-19 were significantly lower than those in patients with other well-recognized cytokine storm syndromes [150] and healthy controls [148,150]. The decrease was associated with the progression of disease, from moderate to critical grade. SR DcR3 levels in patients with hemorrhagic fever with renal syndrome (HFRS) caused by Hantaan virus infection were significantly higher than those in healthy controls, irrespective of disease severity [136]. The DcR3 levels in patients with HFRS depended on the disease phase, with peak values at the oliguric phase. SR sFasL levels in patients with Ebora virus disease (EVD) were significantly higher than those in healthy controls, in contrast, the sFas levels in most patients with EVD fell within the reference range in healthy controls [140]. In patients with myocarditis caused by enterovirus and adenovirus infection, SR sFasL levels after daily treatment with a Chinese herb, *Astragalus mongholicus Bge*, were significantly lower than those in the cases of placebo drug treatment, concomitant with downregulation of immune-regulatory microRNAs, miR-146b and miR-155 [143].

3.3.3. Other non-septic diseases [151–158]

Other non-septic diseases caused by bacterial infections include tuberculosis (TB) [153,154,156,157], malaria [151,152,158], and leptospirosis [155] caused by *Mycobacterium tuberculosis*, *Plasmodium falciparum*, and *Leptospira interrogans*, respectively. Significantly elevated sFasL and DcR3 levels in patients with tuberculous PE have been repeatedly reported in comparison with those in other types of diseases, including malignancy and bacterial parapneumonia [153,156,157]. SR DcR3 levels in patients with active TB were higher than in those with latent TB contacts and noninfected controls [154]. The diagnostic efficacy of PE sFasL levels for tuberculous pleurisy was comparable to that of conventional biomarkers such as interferon (IFN)-γ and adenosine deaminase (ADA) [153], but was not affected by patient age [157]. The low diagnostic sensitivity and specificity of IFN-γ-or ADA alone were substantially improved by the combination with PE DcR3 and soluble TNF receptor 1 levels [156]. PL sFas levels have been suggested as a potential biomarker of severity and mortality in patients with cerebral malaria [152]. SR sFasL levels were the best discriminatory predictor of malaria from bacteremia, which may guide treatment decisions as an innovative point-of-care test in malaria-endemic regions [158]. Increased SR sFasL levels at the time of hospital admission are strongly associated with higher mortality in patients with severe leptospirosis [155].

3.4. Cardiovascular and hematologic systems-specific diseases [159–189]

SR/PL sFas, sFasL, and DcR3 levels have been investigated for their potential use as clinical biomarkers for various cardiovascular system-specific diseases such as acute coronary syndromes (ACS) and heart failure (HF) (Table 4). Regarding diseases classified into ACS such as acute myocardial infarction (AMI) and unstable angina pectoris, SR/PL sFas and DcR3 levels in patients with ACS were significantly higher than in those with stable CAD and non-ACS controls, including healthy subjects as well as patients with non-cardiac chest pain, suggesting that these parameters were useful markers for the diagnostic and prognostic accuracy of ACS [167,169,176,189]. Elevation of sFas levels in patients with ACS was observed regardless of recurrent cardiac events during one-year follow-up after discharge [169]. PL sFasL levels in patients with AMI showed time-dependent increases and decreases after percutaneous transluminal coronary angiography in multiple studies [162,175,178]. However, no significant longitudinal correlation with left ventricular dysfunction during the follow-up period after AMI was observed with PL sFasL levels [172,175]. The SR sFas/sFasL ratio increased in association with disease severity in patients with ACS [167]. After initiation of support by a percutaneously implanted ventricular assist device, AMI-related severe refractory cardiogenic shock patients showed significant increases and decreases in SR sFas and SR sFasL levels, respectively [177].

Table 4. Possible usage of sFas, sFasL, and DcR3 as clinical biomarkers in cardiovascular and hematologic systems-specific diseases, excluding cancers, autoimmune, allergic, and infectious diseases.

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, chronic congestive heart failure (CCHF)	Plasma (PL) sFas levels in patients with CCHF with New York Heart Association (NYHA)-functional class (FC)-I were similar to those in healthy controls (HC), but were significantly lower than in those with CCHF with FC-II, FC-III, and FC-IV. PL sFasL levels were similar among patients with CCHF with any FC and HC. PL sFas levels were significantly higher in patients with an elevated pulmonary artery wedge pressure (PAWP) and a decreased cardiac index (CI) than the levels in those with values within a normal range.	P: 70 (total CCHF) [48 m/ 22 f; (Mn: 65, SEM: 2), NYHA-FC: 20 (FC-I) [14 m/6 f; (63, 4)], 20 (FC-II) [13 m/7 f; (66, 2)], 15 (FC-III) [10 m/5 f; (64, 4)], 15 (FC-IV) [11 m/4 f; (66, 5)], PAWP: normal (< 18 mmHg) (NOR), elevated (≥18 mmHg) (ELE), CI: normal [>2.2 l/min/body surface area (BSA)] (NOR), decreased (≤2.2 l/min/BSA) (DEC), C: 62 (HC) [43 m/19 f; (62, 5)]	PL (sFas/sFasL, ng/ml), ELISA (Mn, SEM): [CCHF-FC: I (2.2/0.44, 0.2/0.01), II (3.1/0.49, 0.2/0.02), III (3.9/0.44, 0.3/0.02), IV (5.1/0.48, 0.6/0.02)], [HC (2.2/0.43, 0.1/0.01)], sFas: [CCHF: PAWP-NOR (ca. 2.8, ca. 0.19), PAWP-ELE (ca. 4.3, ca. 0.39); CI-NOR (ca. 2.8, ca. 0.19), CI-DEC (ca. 4.4, ca. 0.49)]; $p < 0.05$/ns (CCHF-FC-IV vs HC, CCHF-FC: I, II III; CCHF-FC-III vs HC, CCHF-FC: I, II; CCHF-FC-II vs HC, CCHF-FC-I), $p < 0.05$ (sFas) (CCHF-PAWP: NOR vs ELE; CCHF-CI: NOR vs DEC)	[159]
sFas, peripartum cardiomyopathy (PPCM)	Plasma (PL) sFas levels in patients with PPCM were significantly higher than those in healthy controls (HC). PL sFas levels in deceased (DEC) patients were significantly higher than those in survivors (SUV), which deserved further investigation as a predictor of mortality.	P: 29 (total PPCM) [all f; (Mn: 29, SD: 7)], mortality: 8 (DEC), 21 (SUV), C: 20 (HC) (all f; age-matched)	PL (sFas, U/ml), ELISA (Mn, SD): [total PPCM (5.99, 4)], [HC (0.84, 0.21)], [PPCM: DEC (8.98, 4), SUV (5.33, 3)]; $p = 0.0003$ (total PPCM vs HC), $p = 0.02$ (PPCM: DEC vs SUV)	[160]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, chronic heart failure (CHF) (moderate to severe)	A significant reduction of SR sFas and sFasL levels in patients with CHF after the physical training period (PTP) was observed as compared with those in patients during the detraining period (DTP). Despite considerable improvement, SR sFas and sFasL levels in patients with CHF remained higher than the baseline (BS) values of HC. Physical training produced no significant changes in HC. Effects on SR sFasL levels significantly correlated with change (Δ) in peak oxygen consumption (VO_2- max), suggesting that PTP induced an improvement in the functional status of patients with CHF.	P: 24 (CHF) [nd/nd; (Mn: 55, SEM: 2, Rg: 35–70)], C: 20 (HC) (gender- and age-matched), measurement time-points: BS, after 12 weeks PTP, DTP	SR (sFas/sFasL, sFas: ng/ml, sFasL: pg/ml), ELISA (Mn, SEM): [CHF: BS (5.7/35.0, 0.7/5.0), PTP (4.5/25.3, 0.8/4.0), DTP (5.5/34.9, 0.7/5.0)], [HC: BS (2.5/13.5, 0.2/1.0), PTP (2.3/13.0, 0.2/2.0), DTP (2.4/13.8, 0.2/2.0)]; $p < 0.01$/$p < 0.01$ (HC-BS vs CHF: BS, PTP), $p < 0.05$/$p < 0.05$ (CHF: PTP vs BS, DTP), p = ns/p = ns (HC: PTP vs DTP), Corr. (vs Δ in sFasL): $p < 0.005$, $r = -0.57$ (ΔVO_2- max)	[161]
sFasL, acute myocardial infarction (AMI) and angina pectoris (AP)	PL sFasL levels in patients with acute myocardial infarction (AMI) and unstable angina pectoris (UAP) on hospital admission were significantly higher than in those with stable AP (SAP) and healthy controls (HC). Patients with AMI, but not those with SAP, showed a time-dependent increase and decrease in PL sFasL levels after percutaneous transluminal coronary angioplasty (PTCA).	P: 30 (AMI) [23 m/7 f; (Mn: 59, SD: 12)], 10 (UAP) [7 m/3 f; (58, 10)], 10 (SAP) [6 m/4 f; (60, 11)], C: 30 (HC) [21 m/9 f; (56, 8)], measurement time-points (AMI and SAP): 0 (0H), 3 (3H), 6 (6H), 12 (12H), 18 (18H), and 24 (24H) hours after hospital admission (PTCA: performed at 3H)	PL (sFasL, pg/ml), ELISA (Mn): [AMI (ca. 110)], [UAP (ca. 54)], [SAP (ca. 6.7)], [HC (ca. 0)], [AMI: 0H (ca. 81), 3H (ca. 50), 6H (ca. 53), 12H (ca. 93), 18H (ca. 42), 24H (ca. 13)], [SAP: 0H~24H (ca. 9.6-ca. 13)]; $p < 0.01$ (AMI vs HC), $p = 0.0143$ (UAP vs HC), $p = 0.0609$ (UAP vs SAP)	[162]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFasL, familial combined hyperlipidemia (FCH) and carotid atherosclerosis (CAA)	Baseline serum (SR) sFasL levels in patients with FCH and CAA were significantly lower than those in healthy controls (HC). Administration of atorvastatin (ATO) for 6–12 months to patients with FCH, and for 4–6 weeks to patients with CAA, significantly increased SR sFasL levels, reaching normal values in HC. ATO may work for SR sFasL levels in patients with early and late atherosclerosis. A decrease in SR sFasL levels probably indicated endothelial dysfunction, which could be restored by ATO. Treatment with bezafibrate (BEZ) marginally affected SR sFasL levels 12 months after the administration.	P: 58 (total FCH), 28 [ATO-treatment (ATO)] [24 m/4 f; (Mn: 49.9, SD: 11)], 30 [BEZ-treatment (BEZ)] [22 m/8 f; (52.9, 11)], 14 (total CAA), 7 (ATO) [5 m/2 f; (71.5, 6)], 7 [no treatment (NT)] [5 m/ 2 f; (68.6, 9)], C: 15 (HC) (gender- and age-matched), measurement time-points (ATO, BEZ, NT): baseline (BS), after 6 (6M) and 12 months (12M) administration of ATO/BEZ (for FCH), or 4 to 6 weeks (4/6W) administration of ATO/NT (for CAA)	SR (sFasL, pg/ml), ELISA (Md): [total FCH-BS (49)], [FCH-ATO: BS (56), 6M (88), 12M (111)], [FCH-BEZ: BS (46.8), 6M (ca. 37), 12M (85.4)], [CAA-ATO: BS (40), 4/6W (90.7)], [CAA-NT: BS (ca. 32), 4/6W (48.3)], [HC-BS (123)]; $p < 0.0001$ (HC-BS vs total FCH-BS, FCH-ATO-BS, FCH-BEZ-6M; FCH-ATO: BS vs 12M), $p = 0.0103$ (FCH-ATO: BS vs 6M), $p < 0.0005$ (BS: HC vs FCH-BEZ), $p = 0.046$ (FCH-BEZ: BS vs 12M), p = ns (FCH-BEZ: BS vs 6M), $p = 0.02$ (CAA-ATO: BS vs 4/6W)	[163]
sFas, coronary atherosclerosis (CA) and extracoronary atherosclerosis (ECA)	Serum (SR) sFas levels were significantly associated with age and total cholesterol (TC), but were not significantly related to CA and ECA, regarding the presence of coronary calcification (CC), abdominal aortic calcification (AAC), carotid plaques (CP), and peripheral arterial disease (PAD) within a population-based cohort study.	P: 1036 (total CA and ECA) [488 m/548 f; (Mn: 70.7, SD: 5.4)]	SR (sFas, ng/ml), ELISA (Mn, SD): [total CA and ECA (4.9, 1.9)]; linear regression analysis for risk factors (vs sFas): $p < 0.001$, $\beta = 0.04$ (95% CI: 0.03–0.07), (age), $p = 0.02$, $\beta = 0.15$ (95% CI: 0.02–0.27) (TC), p trend for OR (among sFas tertiles): 0.66 (CC), 0.82 (AAC), 0.14 (CP), 0.81 (PAD)	[164]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, coronary heart disease (CHD) at high cardiovascular risk (HCR)	Plasma (PL) sFas and sFasL levels were significantly increased and decreased in patients with CHD at HCR and healthy controls (HC), respectively. PL sFas levels were significantly higher in patients at HCR with hypertension (HYP), metabolic syndrome (METS), and diabetes mellitus (DM), than those in patients without these factors, while PL sFasL levels were significantly low only in patients with METS and HYP. PL sFas and sFasL levels may serve as novel markers for vascular injury. Overall, atorvastatin treatment (ATO) significantly lowered SR sFas levels in patients with CHD patients at HCR compared to SR sFasL levels, however statistical variations among different dosage groups were observed.	P: 1078 [total CHD at HCR (CHD-HCR) [699 m/379 f; (Mn: 63.4, SD: 10.8)], 444 (DM), 534 (non-DM); 506 (MS), 469 (non-MS); 676 (HYP), 294 (non-HY), ATO dosage: 560 [10 mg/day (ATO-10)] [384 m/176 f; (64.2, 10.6)], 149 (ATO-20) [93 m/56 f; (64, 11.3)], 131 (ATO-40) [81 m/50 f; (62.1, 10.8)], 238 (ATO-80) [141 m/97 f; (62, 11)], measurement time-points: baseline (BS) and after ATO treatment for 12 weeks (12W), C: 130 (HC) (gender- and age-matched)	PL (sFas/sFasL, pg/ml), ELISA (Mn): [total CHD-HCR (7392/58.8)], [HC (4640/70.2)], [CHD-HCR: HYP (7495.5/57.9), non-HYP (7159.9/61.2); MS (7626.2/57.3), non-MS (7175.3/60.3); DM (7587.3/57.9), non-DM (7232.7/59.7)]; $p < 0.0001$/$p < 0.0001$ (total CHD-HCR vs HC), CHD-HCR: $p = 0.007$/$p = 0.26$ (DM vs non-DM), $p = 0.0007$/$p = 0.03$ (MS vs non-MS), $p = 0.02$/$p = 0.04$ (HYP vs non-HYP), change in sFas/sFasL (CHD-HCR: BS vs 12W): $p < 0.0001$/$p = 0.04$ (overall ATO), $p = 0.007$/$p = 0.74$ (ATO-10), $p = 0.07$/$p = 0.005$ (ATO-20), $p = 0.001$/$p = 0.29$ (ATO-40), $p = 0.29$/$p = 0.15$ (ATO-80)	[165]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFasL, coronary artery disease (CAD)	Plasma (PL) sFasL levels in patients with CAD were significantly modified with treatment with statins (ST) alone among drugs examined. PL sFasL levels in patients with CAD significantly correlated with changes (Δ) from forearm blood flow (FBF) to forearm reactive hyperemia (FRH), but not with changes from FBF to nitroglycerine (NT), age, body-mass-index (BMI), cholesterols (CH) [total (T), low-density lipoprotein (LDL) and high-density-lipoprotein (HDL)], triglycerides (TG), and glucose (GL).	P: 110 (total CAD) [90 m/20 f; (Mn: 67.5, SD: 11.9)], ST treatment: 84 (ST), 26 (no-ST), other drugs examined: β-blockers (BB), calcium antagonists (CA), angiotensin (AG) converting enzyme inhibitors (AGCEI), AG receptor blockers (AGRB), diuretics (DI), anti-thrombotics (AT) or nitrates (NI)	PL (sFasL, pg/ml), ELISA (Mn, SD): [total CAD (45.4, 15.9)], [CAD: ST (47.1, 15.8), no-ST (38.8, 14.8)]; CAD: $p = 0.02$ (ST vs no-ST), $p = 0.06$ (BB vs no-BB), $p = 0.56$ (CA vs no-CA), $p = 0.41$ (AGCEI vs no-AGCEI), $p = 0.80$ (AGRB vs no-AGRB), $p = 0.12$ (DI vs no-DI), $p = 0.31$ (AT vs no-AT), $p = 0.87$ (NI vs no-NI), Corr. (vs sFasL): $p < 0.001$, $r = 0.324$ (ΔFRH), p = ns (ΔNT, age, BMI, T-CH, LDL-CH, HDL-CH, TG, GL)	[166]
sFas and sFasL, acute coronary syndromes (ACS) [unstable angina (UA), ST-segment elevation myocardial infarction (STEMI), non-STEMI]	Serum (SR) sFas levels were significantly higher among patients with acute coronary syndromes (ACS) than those in patients with stable coronary artery disease (SCAD) and healthy controls (HC). Significant temporal changes of SR sFas and sFasL levels in patients with ACS were observed after hospital admission. SR sFas/sFasL ratios in patients with ACS were significantly higher than those in non-ACS control groups and increased in association with disease severity.	P: 211 (total ACS), 52 (UA) [42 m/10 f; (Mn: 61.4, SD: 10.1)], 87 (non-STEMI) [59 m/28 f; (62.2, 11.7)], 72 (STEMI) [57 m/15 f; (62.9, 11.2)], measurement time-points: within 24 h (<24H) and 48 hours (48H) after hospital admission, C: 105 (total non-ACS), 45 (SCAD) [35 m/10 f; (60.4, 10.4)], 60 (HC) [42 m/18 f; (10.6, 7.2)]	SR (sFas/sFasL, sFas: ng/ml, sFasL: pg/ml), ELISA (Md, Iqr): [UA (7.0/122, 4.0–11.0/101–290)], [non-STEMI (7.9/120, 4.0–12.0/95–285)], [STEMI (6.2/107.5, 4.0–9.0/87.5–148)], [SCAD (4.8/162.5, 3.5–6.1/106–430)], [HC (5.5/125.0, 3.5–8.0/99–290)]; $p = 0.016$/$p = 0.021$ (total ACS vs total non-ACS), $p = 0.004$/$p = 0.003$ (ACS: <24H vs 48H), sFas/sFasL ratio: $p = 0.0004$ (total ACS vs total non-ACS)	[167]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, heart failure (HF) (severe)	Plasma (PL) sFas and sFasL levels and resulting sFas/sFasL ratio in patients with severe HF (SHF) were significantly changed after the short term administration of the inotropic drug milrinone (MIR), which was associated with significant improvements in hemodynamic status assessed by PL N-terminal pro-B-type natriuretic peptide (NTPBNP), but without exacerbation of myocardial necrosis judged by troponin I (TnI) and myoglobin (MYO).	P: 10 (total SHF) [8 m/2 f; (Mn: 52, SD: 17)], drug administration: MIR 0.25–0.5 μg/kg/min (initial dosing), measurement time-points: baseline (BS) and after 24 h (1D) of infusion	PL (sFas/sFasL, pg/ml), ELISA (Rg): [SHF: BS (ca. 1430–ca. 11700/ca. 13.9–ca. 57.8), 1D (ca. 2010–ca. 12100/ca. 14.0–ca. 40.9)]; p = 0.00074/p = 0.044 (SHF: BS vs 1D), sFas/sFasL ratio: p = 0.0016 (SHF: BS vs 1D), myocardial parameters (SHF: BS vs 1D): NTPBNP: p = 0.000011; TnI: p = 0.44; MYO: p = 0.19	[168]
sFas, acute coronary syndromes (ACS)	Plasma (PL) sFas levels in patients with ACS, regardless of recurrent cardiac events during a one-year follow-up after discharge, were significantly higher than those in control subjects with non-cardiac chest pain (non-CCP). Measurements of PL sFas levels helped improve the diagnostic accuracy in the suspected cases of ACS from electrocardiogram (ECG) and necrotic markers (NM).	P: 388 (total ACS), 218 [recurrent (REC)] [152 m/66 f; (Mn: 66, SD: 12)], 170 (non-REC) [121 m/49 f; (65, 12)], C: 100 (non-CCP) [61 m/39 f; (62, 10)]	PL (sFas, pg/ml), ELISA (Md, Iqr): [ACS: REC (ca. 350, ca. 290–ca. 450), non-REC (ca. 369, ca. 280–ca. 470)], [non-CCP (ca. 52, ca. 13–ca. 120)]; p = 0.001 (total ACS vs non-CCP), ROC curve analysis for ACS diagnosis using ECG and NM: AUC = 0.85 (95% CI: 0.82–0.89) (without sFas), AUC = 0.93 (95% CI: 0.91–0.96) (sFas added)	[169]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas, vascular endothelium dysfunction (VED) (male smokers)	Plasma (PL) sFas levels of male smokers (MS) in a high dose green-tea catechins group (HGTC) after 14 days significantly decreased as compared with those in the baseline and catechin-free (GTCF). A significant long-term PL sFas level reduction recorded only in the HGTC MS group was associated with an increase in peak forearm blood flow (FBF) response to reactive hyperemia (RH) (ΔFBF-RH).	P: 30 (total MS), 10 [HGTC (580 mg/day)] [all m; (Mn: 35.3, SD: 2.1)], 10 [middle dose (M) GTC (80 mg/day)] [all m; (37.4, 2.1)], 10 (GTCF) [all m; (35.4, 2.1)], measurement time-points: baseline (BS), after 2 hours (2H), 7 days (7D), and 14 days (14D) GTC administration	PL (sFas, ng/ml), ELISA; P (Mn, SD): [MS-HGTC: BS (0.87, 0.11); 2H (0.86, 0.06); 7D (0.76, 0.06); 14D (0.72, 0.10)], [MS-MGTC: BS (0.74, 0.13); 2H (0.70, 0.12); 7D (0.72, 0.15); 14D (0.71, 0.13)], [MS-GTCF: BS (0.96, 0.04); 2H (0.95, 0.07); 7D (1.04, 0.09); 14D (0.96, 0.07)]; $p < 0.05$ (MS: HGTC-14D vs HGTC-BS, GTCF-14D), ΔFBF-RH: $p < 0.05$ (MS-HGTC: BS vs 2H, 7D, 14D)	[170]
sFas and sFasL, coronary heart disease (CHD) at intermediate risk	A novel model, composed of serum (SR) levels of seven CHD-relevant biomarkers, including sFas, sFasL, and conventional clinical risk factors, was developed in a derivation study, Marshfield Clinic Personalized Medicine Research Project (PMRP), for assessing the true risk of CHD events. The model remained to be an independent predictor after Framingham risk factor (FRF) adjustments. The developed algorithm, CHD Risk Assessment (CHDRA), successfully predicted CHD events among patients at intermediate risk in a validation study, Multi-Ethnic Study of Atherosclerosis (MESA).	P: 1091 (total PMRP cohort) [502 m/589 f; with CHD events during 5 years period (CHD) (Mn: 63.7, SD: 10.6, Rg: 40–80), non-CHD (56.4, 10.9, 40–80)], 681 (total MESA cohort) [361 m/320 f; CHD (67.6, 9.2, 48–84), non-CHD (62.0, 10.0, 44–84)]	SR (sFas/sFasL, pg/ml), MPAA; risk analysis (sFas/sFasL, univariate HRs for 1SD increment in the individuals without events): [PMRP cohort] unadjusted HR = 1.87/0.73 (95% CI: 1.65–2.11/0.67–0.80), FRF-adjusted HR = 1.20/0.92 (95% CI: 1.03–1.39/0.83–1.03); [MESA cohort] risk analysis for CHD events by CHDRA: $p < 0.001$, HR = 2.17 (FRF 5-years intermediate risk patients)	[171]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFasL, acute myocardial infarction (AMI)	Plasma (PL) sFasL levels in patients after one month of myocardial infarction (MI) were not significantly associated with left ventricular (LV) echocardiographic parameters, including change (Δ) in end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction during a one year follow-up period (1Y-FP) after MI. Event-free survival three years after MI did not significantly differ according to the PL sFasL levels at one month.	P: 205 (total AMI), [163 m/42 f; (Mn: 56.5, SD: 13.7)], 68 [1st sFasL tertile (≤40.2 pg/ml) (T1)] [56 m/12 f; (56.5, 11.6)], 68 [2nd sFasL tertile (40.2–60.2 pg/ml) (T2)] [56 m/12 f; (57.0, 13.8)], 69 [3rd sFasL tertile (>60.2 pg/ml) (T3)] [51 m/18 f; (56.1, 15.4)], measurement time-point: 1 month (1M) after MI	PL (sFasL, pg/ml), ELISA (Md, Iqr): [total AMI-1M (50.2, 32.7)]; Corr. (vs sFasL tertiles at 1M, during 1Y-FP): $p = 0.126$, $r = -0.107$ (ΔLV-EDV), $p = 0.07$, $r = -0.128$ (ΔLV-ESV), log rank analysis for cardiovascular death or hospitalization for heart failure at 3 years after MI: $p = 0.510$ (sFasL at 1M: among T1, T2, T3)	[172]
sFas, chronic heart failure (CHF)	Serum (SR) sFas levels in patients with CHF were significantly higher than those in healthy controls (HC). SR sFas levels in patients with CHF significantly correlated with some clinical cardiopulmonary variables, including the New York Heart Association (NYHA)-functional class (FC) and peak oxygen consumption (VO_2- max).	P: 106 (CHF) [84 m/22 f; (Mn: 59.2, SD: 11.9)], C: 39 (HC) [31 m/8 f; (55.1, 10.4)]	SR (sFas, ng/ml), ELISA (Mn, SD): [CHF (3.38, 1.23)], [HC (2.60, 0.88)]; $p = 0.0004$ (CHF vs HC), Corr. (vs sFas): $p = 0.0012$, $r = 0.310$ (NYHA-FC), $p < 0.0001$, $r = -0.287$ (VO_2- max)	[173]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFasL, coronary artery disease (CAD)	SR sFasL levels in patients with CAD were higher than those in normal coronary arteries controls (non-CAD). Hypertension (HYP) and medication with acetylsalicylic acid/clopidogrel (ASA/C) were significantly related to increased SR sFasL levels. SR sFasL levels significantly correlated with the Azar score (AS) and coronary vessel score (CVS). SR sFasL level may be a biochemical surrogate of severe coronary atherosclerosis.	P: 116 (total CAD) [75 m/41 f; (Mn: 60, SD:10)], nd [with hypertension (HYP)], nd (non-HYP); nd [with ASA/C medication (ACM)], nd (non-ACM), C: 53 (non-CAD) [17 m/36 f; (55, 10)]	SR (sFasL, mU/ml), ELISA (Mn, SD): [total CAD (0.52, 0.23)], [non-CAD (0.45, 0.18)], [CAD: HYP (0.60, 0.33), non-HYP (0.52, 0.27); ACM (0.65, 0.38), non-ACM (0.54, 0.27)]; $p = 0.023$ (total CAD vs non-CAD), $p = 0.019$ (CAD: HYP vs non-HYP), $p = 0.016$ (CAD: ACM vs non-ACM), Corr. (vs sFasL): $p = 0.003$, $r = 0.231$ (AS), $p < 0.001$, $r = 0.269$ (CVS)	[174]
sFas and sFasL, ST-elevation myocardial infarction (STEMI)	Plasma (PL) sFas and sFasL levels in patients with ST-elevation myocardial infarction (STEMI) significantly increased and decreased, respectively, during a 24-hour period after primary percutaneous coronary intervention (PCI). PL sFas and sFasL levels in non-STEMI controls did not significantly differ from those in patients with STEMI before PCI. PL sFas and sFasL levels both before and 24 hours after the PCI did not significantly correlate with either infarct size (IS) or left ventricular dysfunction (LVD) 5 days (5D)/4 months (4M) after STEMI.	P: 46 (STEMI) [30 m/16 f; (Mn: 61, SD: 11)], measurement time-points: prior to (PRI) and 24 hours (24H) after primary PCI, C: 32 [non-STEMI (nd/nd; age-matched)]	PL (sFas/sFasL, pg/ml), ELISA (Md, Iqr): [STEMI: PRI (6527/45.3, 5375–8093/35.8–55.0), 24H (7685/43.6, 6146–8655/35.7–51.8)], [non-STEMI (6758/46.7, 6273–7077/43.0–50.8); $p < 0.001$/$p = 0.029$ (STEMI: PRI vs 24H), Corr. (vs sFas/sFasL in STEMI-PRI/24H): p = ns/p = ns (IS, LVD, at 5D/4M after STEMI)	[175]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas, acute coronary syndrome (ACS)	Serum (SR) sFas levels in patients with ACS with a composite end-point (CEP), death or hospitalization for heart failure (HF), within six months follow-up, were higher than those in end-point free patients (non-CEP), but the difference was not statistically significant. SR sFas levels were a significant predictor of the CEP according to univariate, but not multivariate, analysis.	P: 295 (total ACS), 26 (CEP) [20 m/6 f; (Mn: 72.6, SD: 10.8)], 269 (non-C-EP) [192 m/ 77 f; (66.1, 13.4)]	SR (sFas, pg/ml), ELISA (Md, Rg): [ACS: CEP (7440, 5774–9443), non-CEP (6530, 5702–8009)]; p = ns (ACS: CEP vs non-CEP), univariate regression risk analysis for CEP (sFas): p = 0.018, OR = 6.77, (95% CI: 1.39–32.78) (death or hospitalization for HF), p = 0.056, OR = 8.21 (95% CI: 0.67–100.2) (death)	[176]
sFas and sFasL, severe refractory cardiogenic shock (SRCS)	Baseline serum (SR) sFas and sFasL levels in patients with SRCS were within normal ranges. Compared with the baseline, significant increases and decreases in SR sFas and SR sFasL levels, respectively, were observed at 24 hours and 7 days from receiving percutaneously implanted ventricular assist device (PVAD).	P: 21 (SRCS) [17 m/4 f; (Mn: 52.43, SD: 17.37)], measurement time-points: baseline (BS), at 24 hours (24H) and 7 days (7D) of PVAD support	SR (sFas/sFasL, pg/ml), ELISA (Md, Iqr): [SRCS: BS (7749/43.6, 6196–12054/33.1–77.6), 24H (9809/35.1, 8589–13480/29.4–43.0), 7D (12268/34.6, 9073–15106/24.2–38.0)], p = 0.0129/p = 0.0015 (SRCS: BS vs 24H), p = 0.0046/p = 0.0159 (SRCS: BS vs 7D)	[177]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, coronary artery disease (CAD) [non-ST elevation acute coronary syndrome (non-STE-ACS) and stable angina (SA)]	In cohort I (CI), plasma (PL) sFasL, but not sFas, levels prior to coronary angiography (CAG) in patients with non-STE-ACS were significantly lower than those in patients with SA or healthy controls (HC). Longitudinal analysis of CI (CI-L) revealed an increasing trend in PL sFasL, but not sFas, levels in a combined patient group with non-STE-ACS and SA. In cohort-II (CII), both PL sFas and sFasL levels in patients with non-STE-ACS at 3–6 months after a coronary event (non-STE-ACS-3/6M) were not significantly different from those in HC.	[CI] P: 65 (total CAD), 31 (non-STE-ACS) [23 m/8 f; (Md: 69, Rg: 50–83)], 34 (SA) [28 m/6 f; (63, 44–77)], [CI-L (n = 43)] P: 15 (non-STE-ACS) plus 28 (SA), measurement time-points: 1 day prior to (PRI), 3 months (3M), 12 months (12M) after CAG, C: 37 (HC) [28 m/9 f; (63, 45–77)]; [CII] P: 16 (non-STEACS-3/6M) [14 m/2 f; (60, 58–65)], C: 16 (HC) [14 m/2 f; (60, 55–62)]	PL (sFas/sFasL, pg/ml), ELISA (Md, Iqr): CI-PRI: [non-STE-ACS (7308/49, 6235–8364/35–52), SA (7010/54, 6347–8134/39–64), HC (7546/52, 6414–8611/43–74)], CI-L: [PRI (7275/51, 6332–8279/37–60), 3M (7849/55, 6451–8790/42–63), 12M (7746/57, 6848–8869/43–70)], CII: [non-STE-ACS-3/6M (8087/55, 6932–8845/48–66)], [HC (7187/57, 6261–8035/48–63)]; p = ns/p < 0.05 (CI: non-STE-ACS vs SA, HC), p = 0.689/p < 0.001 (CI-L: among PRI, 3M, 12M), p = 0.216/p = 0.926 (CII: non-STE-ACS-3/6M vs HC)	[178]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, heart failure (HF)	Serum (SR) sFas levels in patients with HF treated with a highly selective, vasodilative β-1 antagonist, nebivolol (NEB), increased less compared to those in patients with HF treated with placebo (PL) during a 6 –12 months' follow-up. SR sFasL levels showed a decreasing trend in patients with HF treated with PL, but in those with HF treated with NEB remained almost constant. However, the difference in neither SR sFas nor SR sFasL levels at the same time-point was statistically significant.	P: 75 (total HF) [44 m/31 f; (Mn: 75.2, SD :3.9, Md: 75.2)], 36 (NEB) [18 m/18 f; (75.9, 3.7, 75.7)], 39 (PL) [26 m/13 f; (74.5, 3.9, 74.2)], measurement time-points: baseline (BS), 6 months (6M), 12 months (12M) after drug treatment	SR (sFas/sFasL, pg/ml), ELISA (Mn, SD): [HF-NEB: BS (2807/71.7, 1600/98.7), 6M (2682/70.8, 1626/93.9), 12M (2992/71.7, 1208/70.4)], [HF-PL: BS (2687/76, 1409/81.7), 6M (3117/53.7, 2054/45.4), 12M (3584/51.9, 1646/53)]; $p = 0.303/p = 0.252$ (HF-6M: NEB vs PL), $p = 0.077/p = 0.183$ (HF-12M: NEB vs PL)	[179]
DcR3, coronary artery disease (CAD)	Serum (SR) DcR3 levels were significantly higher in patients with severe CAD with high Syntax score (SS) than those in patients with intermediate and low SS. SR DcR3 levels were an independent risk factor for high SS. SR DcR3 levels were a good predictor for the cumulative incidence of major adverse cardiovascular events (MACE)-free survival (SUV), myocardial infarction (MI), and revascularization (REV), but not for all-cause mortality (MOR), in patients with CAD.	P: 152 (total CAD) [110 m/42 f; (Mn: 72.5, SD:11.7)], 51 [low (≤ 13) SS (LSS)] [37 m/14 f; (72.0, 10.4)], 51 [intermediate (>13 and <22) SS (ISS)] [37 m/14 f; (72.9, 13.0)], 50 [high (>22) SS (HSS)] [36 m/14 f; (72.7, 11.8)]	SR (DcR3, pg/ml), ELISA (Mn, SD): [CAD: LSS (4637, 4403), ISS (8025, 7789), HSS (13602, 7256)]; $p < 0.001$ (among LSS, ISS, HSS), risk analysis for HSS diagnosis (per 1000 pg/ml of DcR3) (unadjusted/adjusted for other risk factors): $p < 0.001/p < 0.001$, OR = 1.14/OR = 1.15 (95% CI: 1.08–1.20/1.09–1.21), log-rank analysis (among DcR3 tertiles): $p < 0.001$ (MACE-free SUV, fatal and non-fatal MI, REV), $p = 0.326$ (MOR)	[180]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, sickle cell disease (SCD) (pediatric and adolescent)	Serum (SR) sFas levels were significantly higher, while SR sFasL levels were lower, in patients with pediatric/adolescent sickle cell disease (SCD) than those in healthy controls (HC). Patients with pulmonary hypertension (PH), sickle crisis (SC), and nephropathy (NE) had significantly higher sFas/sFasL ratios (sFR/sFL), but patients treated with hydroxyurea (HU) had lower sFR/sFL ratios. sFR/sFL could detect patients with SCD with PH or NE efficiently. sFR/sFL was a biomarker for vascular dysfunctions and may be reliable in the assessment of renal impairment in patients with SCD.	P: 35 (total SCD) [23 m/12 f; (Mn: 8.4, SD: 3.69, Rg: 3–15)], 11 (PH), 24 (non-PH); 12 [SC > 3 attacks/year (SC)], 23 (non-SC); 19 (NE), 16 (non-NE), 24 [received HU (10–25 mg/kg/day) (HU)], 11 (non-HU), C: 35 (HC) [16 m/19 f; (9.1, 3.2, 5–16)]	SR (sFas/sFasL, pg/ml), ELISA (Md, Iqr): [total SCD (1400/130, 1300–2200/100–220)], [HC (1000/200, 400–1400/160–340)], sFR/sFL (Md): [SCD: non-PH (ca. 7.2), PH (ca. 30); non-SC (ca. 6.2), SC (ca. 28); non-NE (ca. 7.3), NE (ca. 15); non-HU (ca. 32), HU (ca. 7.7)]; $p < 0.001$/$p = 0.022$ (total SCD vs HC), sFR/sFL: $p < 0.001$ (total SCD vs HC), ROC curve analysis for sick-symptom detection (sFR/sFL): AUC = 0.926 (CV = 22) (PH), AUC = 0.924 (CV = 8.75) (NE)	[181]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas, cardiovascular diseases (CVD) [subarachnoid hemorrhage (SUH), intra-parenchymal hemorrhage (IPH), ischemic stroke (IS), coronary heart disease (CHD)]	Serum (SR) sFas levels in patients with SUH and IPH were significantly higher than those in corresponding controls for each disease. 1-SD increment in serum (SR) sFas levels significantly correlated with mortality from SUH among middle-aged patients with CVD enrolled in a Japan Collaborative Cohort (JACC) study. SR sFas levels had a potential role in the development or prognosis of SUH. No significant association of SR sFas levels was observed with mortality from total stroke (TS), IPH, IS or CHD.	P: 233 (TS) [120 m/113 f; (Mn: 67.7, SD: 8.1)], 49 (SUH) [18 m/31 f; (61.9, 9.7)], 55 (IPH) [28 m/27 f; (66.6, 7.8)], 71 (IS) [44 m/27 f; (70.3, 6.4)], 97 (CHD) [53 m/44 f; (67.3, 7.6)], C: 233 (for TS) [120 m/113 f; (67.0, 7.5)], 49 (for SUH) [18 m/31 f; (61.8, 9.4)], 55 (for IPH) [28 m/27 f; (66.3, 7.5)], 71 (for IS) [44 m/27 f; (69.1, 5.5)], 97 (for CHD) [53 m/47 f; (66.9, 7.3)]	SR (sFas, ng/ml), ELISA (Mn, SD): [TS: patient (P) (2.4, 1.4), control (C) (2.2, 1.3)], [SUH: P (2.3, 1.4), C (2.0, 1.3)], [IPH: P (2.6, 1.4), C (2.4, 1.3)], [IS: P (2.4, 1.4), C (2.3, 1.4)], [CHD: P (2.2, 1.4), C (2.2, 1.3)]; $p < 0.05$ (SUH: P vs C; IPH: P vs C), risk analysis for mortality (per 1-SD = 1.3 ng/ml increment of sFas, after adjustment for cardiovascular risk factors): $p = 0.04$, OR = 4.04 (1.07–15.3) (SUH), $p = 0.12$ (TS), $p = 0.75$ (IPH), $p = 0.13$ (IS), $p = 0.56$ (CHD)	[182]
sFas, cardiovascular diseases (CVD) with/without diabetes mellitus (DM)	Patients with non-DM with incident CVD had significantly higher baseline plasma (PL) sFas levels than those in patients who remained free of CVD. No significant differences were observed between patients with and without CVD with DM at baseline. Patients with higher tertiles of PL sFas levels had increased risks of cardiovascular death (CD), acute myocardial infarction (AMI), and ischemic stroke (IS).	P: 627 (total CVD), 95 [with DM (DM)] [58 m/37 f; (Mn: 61, SD: 4.77)], 532 (non-DM) [291 m/241 f; (60.27, 5.30)], C: 4115 (total non-CVD), 268 (DM) [147 m/121 f; (58.57, 5.79)], 3847 (non-DM) [1399 m/2448 f; (56.95, 5.9)]	PL (sFas, arbitrary units), MPAA (PEA) (Mn, SD): [CVD: DM (189, 63), non-DM (177, 67)], [non-CVD: DM (185, 79), non-DM (166, 93)]; $p < 0.0001$ (non-DM: CVD vs non-CVD), $p =$ ns (DM: CVD vs non-CVD), log-rank test for cumulative event-free survival (among sFas tertiles): $p < 0.0001$ (CD, AMI), $p < 0.05$ (IS)	[183]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
DcR3, coronary artery disease (CAD) (advanced) [impairment in coronary collateral circulation (CCC)]	Plasma (PL) DcR3 levels were significantly higher in patients with advanced CAD (≥90% diameter stenosis in at least one coronary artery) with good CCC than those in patients with poor CCC and positively correlated with the Rentrope Cohen classification grade (RCCG) for the collateral degree. PL DcR3 levels significantly correlated with vascular endothelial growth factor (VEGF)-A, but not with vascular cell adhesion molecule (VCAM)-1, and displayed potent predictive power for CCC status.	P: 92 (total CAD), 48 [good (RCCG: 2 or 3) CCC (GCCC)] [16 m/32 f; (Mn: 63.56, SD: 9.14)], 44 [poor (RCCG: 0 or 1) CCC (PCCC)] [15 m/29 f; (61.34, 7.529)]	PL (DcR3, ng/l), ELISA (Mn, SD): [CAD: GCCC (328.00, 230.82), PCCC (194.84, 130.63)]; $p = 0.001$ (GCCC vs PCCC), Corr. (vs DcR3): $p < 0.01$, $r_s = 0.292$ (RCCG), $p < 0.01$, $r_s = 0.409$ (VEGF-A), $p = 0.222$, $r_s = 0.129$ (VCAM-1), ROC curve analysis for prediction of CCC status (DcR3): $p = 0.016$, AUC = 0.668 (95% CI: 0.532–0.761)	[184]
DcR3, coronary artery disease (CAD) with coronary artery bypass grafting (CABG) (severe)	Plasma (PL) DcR3 levels in patients with severe CAD undergoing CABG treatment (CAD) were significantly higher than those in non-CAD controls. PL DcR3 levels significantly correlated with the presence of CAD. PL DcR3 levels may be a useful biomarker for diagnosing severe CAD. Combination of PL DcR3 levels with tumor necrosis factor-like cytokine (TL) 1A levels improved predictive performance for CAD.	P: 40 (CAD) [22 m/18 f; (Mn: 61.8, SD: 7.2)], C: 37 (non-CAD) [25 m/12 f; (57.4, 8.7)]	PL (DcR3, ng/ml), ELISA (Mn, SD): [CAD (15.3, 6.0)], [non-CAD (7.3, 3.0)]; $p < 0.001$ (CAD vs non-CAD), risk analysis for CAD (DcR3): $p = 0.001$, OR = 1.8 (95% CI: 1.3–2.6) (adjusted for other risk factors), ROC curve analysis for CAD diagnosis: $p < 0.001$, AUC = 0.899 (95% CI: 0.833–0.965) (DcR3 alone), $p < 0.001$, AUC = 0.944 (DcR3 and TL1A) (95% CI: 0.898–0.991)	[185]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
DcR3, coronary heart disease (CHD)	Serum (SR) DcR3 levels in patients with CHD were significantly lower than those in healthy controls (HC). SR DcR3 levels in patients with CHD decreased as disease severity increased. SR DcR3 levels may predict CHD and prognosis of patients with CHD.	P: 242 (total CHD) [115 m/127 f; (Rg: 27–56)], [primary disease (PRI), moderate disease (MOD), severe disease (SEV)], C: 103 (HC) [49 m/54 f; (28–63)]	SR (DcR3, μmol/l), ELISA (Mn, SD): [CHD: SEV (ca. 42, ca. 2.3), MOD (ca. 81, ca. 3.1), PRI (ca. 120, ca. 7.7)], [HC (ca. 220, ca. 10)]; $p < 0.01$ (CHD: SEV vs MOD; CHD-MOD vs CHD-PRI, HC)	[186]
sFasL, fatal heart failure (FHF), congenital heart defects (CHDE), arrhythmias (AR) (fetus)	Maternal serum (SR) sFasL levels in fetus patients at 28–33 gestational weeks (GW) with fatal heart failures (FHF) as assessed by a cardiovascular profile score (CVPS) were significantly higher than those in non-FHF controls. SR sFasL levels were classified into the first component group by principal component analysis of patients with FHF, but was not an independently associated factor.	P: 50 (total FHF), 37 (CHDE), 13 (AR), C: 61 (total non-FHF), 10 (CHDE), 6 (AR), 45 healthy controls (HC)] [parent f; (nd)], P and C: 67 [total fetuses in 28-33 GW (FET-28/33GW)], 6 (CVPS ≤7) [parent f; (Mn: 31.6, SD: 2.9)], 61 (CVPS ≥8) [parent f; (33.6, 4.9)]	Maternal SR (sFasL, pg/ml), MPAA (Mn, SD): [FET-28/33GW-CVPS: ≤7 (539.0, 346.2), ≥8 (367.5, 141.8)]; $p = 0.02$ (FET-28/33GW-CVPS: ≤7 vs ≥8), risk analysis for FHF (sFasL): $p = 0.04$, OR = 1.00 (95% CI: 1.00–1.01) (univariate analysis)	[187]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
sFas and sFasL, coronary artery disease (CAD) and acute coronary syndrome (ACS)	Serum (SR) sFas and sFasL levels were included as biomarker components in the CAD predictive algorithm (CADPA), defined by the % future risk of ACS in five years. A subgroup of discordant (DS) patients, who scored high risk (HR) on CADPA, but the low risk (LR) or intermediate risk (IR) on the conventional 5-year modified Framingham global risk (5YmFR) assessment, was identified. SR sFas and sFasL levels were the strongest predictors of DS between CADPA and 5YmFR.	P: 2362 (total CADPA) [1343 m/1019 f; (Mn: 61.7, SD: 13.2)], CADPA risk: 694 [LR (0–3.49 %)] [303 m/391 f; (50.1, 10.6)], 606 [IR (3.5–7.49 %)] [329 m/277 f; (61.0, 9.9)], 1062 [HR (>7.5%)] [711 m/351 f; (69.8, 10.2)]; discordance from 5YmFR: 959 (DS) [610 m/349 f; (69.4, 10.3)], 1403 (non-DS) [733 m/670 f; (56.5, 12.3)]	SR (sFas and sFasL, nd), nd; risk analysis for DS between CADPA and 5YmFR (sFas/sFasL): $p < 0.01$/$p < 0.01$, OR = 2.19/0.50 (95% CI: 1.86–2.58/0.43–0.57)	[188]
DcR3, acute myocardial infarction (AMI) and stable angina pectoris (SAP)	Serum (SR) DcR3 levels in male patients with AMI were significantly higher than those in patients with SAP and non-cardiovascular disease (non-CAD) controls, even after adjustment for the body-mass-index (BMI), waist-hip-ratio (WHR), interleukin (IL)-6 levels, and white blood cells count (WBC). Significant positive correlations between SR DcR3 levels and relevant clinical indices in patients with CAD, including Gensini score (GS) and epicardial fat thickness (EFT), were found.	P: 30 (AMI) [all m; (Mn: 62.13, SD: 13.22), 30 (SAP) [all m; (63.00, 8.44)], C: 30 (non-CAD) [all m; (62.13, 13.22)]	SR (DcR3, ng/ml), ELISA (Mn, SD): [AMI (7.72, 4.25)], [SAP (5.95, 2.66)], [non-CAD (4.45, 1.10)]; $p < 0.05$ (AMI vs SAP, non-CAD, unadjusted), $p < 0.001$ (AMI vs SAP, non-CAD; SAP vs non-CAD, adjusted for BMI, WHR, IL-6, WBC), Corr. (vs DcR3 in CAD patients): $p < 0.001$, $r_s = 0.48$ (GS), $p < 0.001$, $r_s = 0.401$ (EFT)	[189]

Concerning the progression of cardiovascular diseases caused by blood vessel stenosis, SR sFasL levels in patients with CAD were significantly higher than those in non-CAD controls [174]. The sFasL levels showed a significantly positive correlation with the coronary vessel score, indicating coronary atherosclerotic burden on the coronary artery vessels. Conversely, SR sFasL levels in patients with familial hyperlipidemia and carotid atherosclerosis are significantly lower than those in healthy controls [163]. In this case, the decrease in sFasL levels probably indicated endothelial dysfunction, which was effectively restored after atorvastatin treatment. In this regard, among the several different types of drugs examined, PL sFasL levels in patients with CAD were significantly modified by treatment with statins alone [166]. SR DcR3 levels in patients with CAD reflected the degree of stenosis of coronary artery vessels, and the DcR3 level was identified as a good predictor of the cumulative incidence of major adverse cardiovascular event-free survival [180]. PL DcR3 levels in patients with advanced CAD with good coronary collateral circulation (CCC) and DcR3 levels in patients with severe CAD undergoing coronary artery bypass grafting (CABG) were significantly higher than those in patients with poor CCC [184] and non-CAD controls [185], respectively. In contrast, SR sFas levels exhibited no evident association with coronary calcification or carotid plaques, even though they were significantly correlated with age and total cholesterol level [164]. SR sFas levels in patients with subarachnoid hemorrhage (SUH) or intraparenchymal hemorrhage (IPH) were significantly higher than those in individual control subjects [182]. A significant association between a 1-SD increment in the SR sFas levels and mortality was observed for SUH, but not for IPH, ischemic stroke (IS), or coronary heart disease (CHD). In addition, SR DcR3 levels in patients with CHD decreased as disease severity increased, suggesting that the DcR3 levels may be a predictor of CHD and prognosis of patients with CHD [186].

The interrelation between sFas and sFasL levels and other conventional clinical risk factors for cardiovascular diseases (CVD), including CHD, have been investigated using relatively large cohorts [165,171,183,188]. Baseline PL sFas levels were significantly higher in patients with CHD at high cardiovascular risk, with hypertension (HYP), metabolic syndrome (METS), or diabetes mellitus (DM), than the levels in those without these factors, while a statistical difference was observed for patients with HYP or METS alone regarding PL sFasL levels [165]. Non-DM cases with incident CVD had significantly higher baseline PL sFas levels than those who remained free of CVD, and patients with high sFas levels had an increased risk for AMI, cardiovascular death, and IS [183]. Advanced algorithms for the risk assessment of either CHD or ACS incidence over five years, including SR sFas and sFasL levels as the biomarkers, have been recently developed [171,188]. A comparison of the redesigned algorithm for ACS with a conventional risk assessment algorithm named 5-year modified Framingham global risk assessment revealed that SR sFas and sFasL levels were the strongest predictors for identification of the discordant patient subgroup [188].

SR/PL sFas, but not sFasL, levels in patients with chronic HF were significantly higher than those in healthy controls if they were at a more severe stage than FC-II assessed using the New York Heart Association functional class criteria [159,173]. SR sFas levels showed a significant negative correlation with clinical cardiopulmonary parameters and peak oxygen consumption (VO_2-max) [173]. Concerning drug treatments, changes in PL/SR sFas and sFasL levels in patients with HF were associated with the therapeutic effects of the inotropic drug milrinone [168] as well as the vasodilative β-1 antagonist nebivolol [179]. Physical training also caused a significant reduction in SR sFas and sFasL levels in patients with chronic HF, accompanied by an improvement in VO_2-max; however, the levels remained higher than those in healthy controls even after the training period [161]. Maternal SR

sFasL levels in fetus patients suffering from fatal HF, judged by the cardiovascular score, were markedly elevated compared with those in non-fatal HF controls [187].

Other relevant disorders in this category include peripartum cardiomyopathy (PPCM), vascular endothelium dysfunction (VED) in male smokers, and a hematologic system disease called sickle cell disease (SCD). Baseline PL sFas levels in PPCM patients, especially those in deceased patients due to progression of HF, were significantly higher than those in healthy controls [160]. Long-term administration of high-dose green tea catechins significantly reduced PL sFas levels in male smokers, concomitant with the amelioration of VED [170]. SR sFas and SR sFasL levels in pediatric and adolescent patients with SCD were significantly higher and lower, respectively, than those in healthy controls [181]. The SR sFas/sFasL ratio could efficiently detect patients with pulmonary hypertension and nephropathy, suggesting its usefulness as a biomarker for assessing vascular dysfunction and renal impairment in patients with SCD.

3.5. Non-cardiovascular/hematologic systems-specific diseases [190–231]

The survey results in this section are summarized in Table 5.

3.5.1. Renal system diseases [190–200]

PL/SR sFas and DcR3 levels and less frequently SR sFasL levels in patients with dialysis-dependent end-stage renal disease (ESRD)/chronic kidney disease (CKD) or non-dialysis-dependent CKD have been widely investigated in terms of disease severity as well as their correlations with SR levels of other biomarkers. The sFas levels in patients with ESRD on hemodialysis (HD) and in those with non-dialysis-dependent CKD were substantially higher than those in healthy controls [191], and sFas levels increased with the disease progress after entering CKD stage 3 [193]. PL sFas levels in patients with ESRD on HD accompanied by peripheral arterial occlusive disease [190] and SR DcR3 levels in patients with ESRD on chronic peritoneal dialysis with peritonitis [192] were significantly elevated compared to those in patients lacking individual disease symptoms. SR sFas levels in patients with non-dialysis-dependent CKD with anemia requiring erythropoietin-stimulating agent (ESA) therapy were significantly higher than those in patients who did not require ESA therapy [200]. The presence of carotid artery plaques did not significantly influence the PL sFas levels in patients with CKD at stages 3–5 [197]. SR sFas levels in patients with ESRD on HD and non-dialysis-dependent CKD positively correlated with the SR levels of C-reactive protein (CRP) and creatine but negatively correlated with those of albumin [191]. SR DcR3 levels in patients with CKD on HD correlated with several SR inflammation biomarkers, including IL-6 and high-sensitivity CRP, and DcR3 levels were an independent predictor of cardiovascular and all-cause mortality in these patients [194]. In addition, SR/PL sFas levels in non-dialysis and dialysis-dependent CKD showed a significant positive correlation with SR erythropoietin (EPO) levels [200] and the levels of some uremic toxins represented by indoxyl sulfate [197], and a significant negative correlation with SR hemoglobin (Hb) levels [200] and estimated glomerular filtration rate (eGFR) [197,200]. In contrast, no significant association of both SR sFas and sFasL levels with Hb levels, caused by EPO derivative treatment in CKD stage 4 patients, was observed in another study [195].

Table 5. Possible usage of sFas, sFasL, and DcR3 as clinical biomarkers in non-cardiovascular/hematologic systems-specific diseases excluding cancers, autoimmune, allergic, and infectious diseases.

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Renal system diseases (excluding transplantation)				
sFas, end-stage renal disease (ESRD) on hemodialysis (HD) with peripheral arterial occlusive disease (PAOD)	Plasma (PL) sFas levels in patients with ESRD on HD (HDESRD) with PAOD were significantly higher than those in patients without PAOD. Increasing PL sFas levels may be a novel and independent biomarker predicting the risk of PAOD-associated atherosclerosis in both lower-extremity (LE) and cerebrovascular system (CVS) in patients with HDESRD.	P: 107 (total HDESRD), 51 [with PAOD (PAOD)] [35 m/16 f; (Mn: 70.7, SD: 10.7)], 56 (non-PAOD) [25 m/31 f; (65.6, 12.8)]	PL (sFas, ng/ml), ELISA (Mn, SD): [HD: PAOD (30.0, 8.9), non-PAOD (26.4, 9.5)]; $p = 0.04$ (HD: PAOD vs non-PAOD), risk analysis for PAOD (per increase of one quintile in sFas, adjusted): $p = 0.01$, OR = 1.69 (95 % CI: 1.09–2.63) (overall), $p = 0.02$, OR = 1.68 (LE), $p = 0.02$, OR = 1.62 (CVS)	[190]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Renal system diseases (excluding transplantation)				
sFas, end-stage renal disease (ESRD) on hemodialysis (HD) and non-dialysis dependent chronic kidney disease (NDDCKD)	SR sFas levels in patients with ESRD on HD (HDESRD) and patients with NDDCKD were significantly higher than those in healthy controls (HC). SR sFas levels in patients with HDESRD, but not in those with NDDCKD and HC, significantly increased during a work-up period. SR sFas levels in both patient groups positively correlated with C-reactive protein (CRP), SR creatinine (CRE), and negatively correlated with SR albumin (ALB). SR sFas levels may become a disease severity biomarker in patients with HDESRD and NDDCKD.	P: 60 (total HDESRD and NDDCKD), 30 (HDESRD) [17 m/13 f; (Mn: 46.7, SD: 6.8)], 30 (CKD) [16 m/14 f; (49.3, 8.3)], C: 30 (HC) [15 m/15 f; (45.1, 9.5)], measurement time-points: baseline (BS) and after 12 months of following work-up period (12M)	SR (sFas, ng/ml), ELISA (Mn, SD): [HDESRD: BS (18.9, 3.2), 12M (23.1, 3.9)], [NDDCKD: BS (12.3, 1.2), 12M (12.5, 1.2)], [HC: BS (5.4, 1.1), 12M (5.6, 1.3)]; $p < 0.001$ (BS, 12M: among HDESRD, NDDCKD, HC), $p = 0.01$ (HDESRD: BS vs 12M), $p = 0.3$ (NDDCKD: BS vs 12M), $p = 0.2$ (HC: BS vs 12M), Corr. (vs sFas, HDESRD/NDDCKD): $p < 0.001$/$p < 0.001$, $r = 0.804$/$r = 0.698$ (CRP), $p = 0.005$/$p = 0.002$, $r = 0.462$/$r = 0.659$ (CRE), $p = 0.009$/$p = 0.007$, $r = -0.464$/$r = -0.659$ (ALB)	[191]
DcR3, end-stage renal disease (ESRD) on chronic peritoneal dialysis (CPD) with peritonitis (PEN)	Serum (SR) DcR3 levels in patients with ESRD on CPD (CPDESRD) with peritonitis (PN) were significantly higher than those in patients free of PN. High SR DcR3 levels (>1.8 ng/ml) and low SR DcR3 levels (<1.8 ng/ml) were significantly associated with increased risks of CPD-related PN onset and PN-free survival in CPDESRD patients, respectively.	P: 77 (total CPDESRD) [35 m/42 f; (Mn: 58, SD: 13)], 15 [with PN (PN)] [7 m/8 f; (58.4, 11.4)], 62 (non-PN) [31 m/ 31 f; (57.9, 12.3)]	SR (DcR3, ng/ml), ELISA (Mn, SD): [CPDESRD: PN (2.63, 1.67), non-PN (1.78, 1.05)]; $p = 0.01$ (CPDESRD: PN vs non-PN), risk analysis for PN (DcR3: >1.8 vs <1.8, adjusted): $p = 0.03$, HR = 3.61 (95 % CI: 1.17–11.08), log-rank test for PN-free survival (DcR3: >1.8 vs <1.8): $p = 0.016$	[192]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Renal system diseases (excluding transplantation)				
sFas and sFasL, chronic kidney disease (CKD) (stages 1–4)	Serum (SR) sFas, but not sFasL, levels in patients with CKD increased with increasing disease severity during CKD stages 1–4. This alteration evidently occurred after CKD patients entered stage 3. SR sFas levels in patients with CKD was a significant indicator of CKD disease severity.	P: 152 (total CKD) [83 m/69 f; (Mn: 64, SD: 12)], 19 [stage 1 (S1)] [8 m/11 f; (58, 11)], 39 [stage 2 (S2)] [21 m/18 f; (63, 10)], 54 [stage 3 (S3)] [33 m/21 f; (65, 13)], 40 [stage 4 (S4)] [21 m/19 f; (68, 11)]	SR (sFas/sFasL, pg/ml), ELISA (Mn, SD): [total CKD (10900/79, 275/32)], [CKD: S1 (9176/72, 746/23), S2 (8542/79, 369/31), S3 (11423/80, 403/34), S4 (13462/81, 461/35)]; $p < 0.001$/p = ns (CKD: among S1, S2, S3, S4)	[193]
DcR3, chronic kidney disease (CKD) on hemodialysis (HD)	Serum (SR) DcR3 levels in patients with CKD on HD (HDCKD) significantly correlated with several inflammation biomarkers, interleukin (IL)-6, high-sensitivity C-reactive protein (hs-CRP), intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1. SR DcR3 levels were an independent predictor of cardiovascular and all-cause mortality in patients with HDCKD.	P: 316 (HDCKD) [150 m/166 f; (Mn: 59)], 106 [high DcR3 tertile (HDcR3)] [50 m/56 f; (Mn: 61, SD: 13)], 105 [middle DcR3 tertile (MDcR3)] [52 m/54 f; (59, 14)], 105 [low DcR3 tertile (LDcR3)] [48 m/57 f; (58, 12)]	SR (DcR3, ng/ml), ELISA (Rg): [HDcR3 (2.45–17.78)], [MDcR3 (0.94–2.41)], [LDcR3 (0.05–0.92)]; Corr. (vs DcR3): $p < 0.001$, $r = 0.32$ (IL-6), $p = 0.01$, $r = 0.14$ (hs-CRP), $p = 0.008$, $r = 0.20$ (ICAM-1), $p = 0.002$, $r = 0.24$ (VCAM-1), risk analysis for mortality (log DcR3, per 1-SD increment): $p < 0.05$, HR = 1.4 (cardiovascular cause), $p = 0.04$, HR = 1.3 (all cause)	[194]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Renal system diseases (excluding transplantation)				
sFas and sFasL, chronic kidney disease (CKD) (stage 4)	Serum (SR) sFas and sFasL levels in stage-4 CKD (CKD-S4) patients were significantly higher than those in healthy controls (HC) before and after anemia treatment with methoxy polyethylene glycol-epoetin beta (MPG-EPO). No significant correlation of either SR sFas or sFasL levels with SR hemoglobin (Hb) level was observed in patients with CKD-S4 before/after MPG-EPO treatment.	P: 35 (CKD-S4) [20 m/15 f; (Md: 59, Rg: 45–69)], measurement time-points: before (BE) and after (AF) MPG-EPO treatment (MET) (n = 25), C: 20 (HC) [12 m/8 f; (56, 48–63)]	SR (sFas/sFasL, pg/ml), ELISA (Md, Iqr): [CKD-S4: BE-MET (3272/85.9, 2734–3799/68.0–109.9), AF-MET (3206/94.3, 2826–3715/75.6–103.8)], [HC (465.0/47.0, 368.0–645.0/30.5–80.0)]; $p < 0.05$/$p < 0.05$ (CKD-S4: BE-MET, AF-MET vs HC), Corr. (sFas/sFasL vs Hb): p = ns/p = ns (CKD-S4: BE-MET, AF-MET)	[195]
sFas, acute kidney injury (AKI) (critically ill)	Plasma (PL) sFas levels in patients critically ill with AKI exhibiting a non-resolving subphenotype (non-RS) were significantly higher than those in patients exhibiting a resolving subphenotype (RS) and non-AKI controls. PL sFas levels were the only biomarker significantly associated with non-RS-AKI after adjustment for age, diabetes mellitus (DM), body mass index (BMI), and the acute physiology and chronic health evaluation III (APACHE-III) score.	P: 868 (total AKI), 502 (RS) [323 m/179 f; (Mn: 55, SD: 15)], 366 (non-RS) [250 m/116 f; (55, 17)], C: 373 (non-AKI) [233 m/140 f; (53, 17)]	PL (sFas, pg/ml), MPAA (Md, Iqr): [AKI: non-RS (12879, 8983–17682), RS (11586, 8095–15700)], [non-AKI (8810, 6880-11926)]; $p < 0.001$ (AKI: non-RS vs RS), risk analysis for non-RS-AKI (per doubling of sFas, adjusted for age, DM, BMI, and APACHE-III score): p = 0.005, RR = 1.16 (95% CI: 1.05–1.28)	[196]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Renal system diseases (excluding transplantation)				
sFas, chronic kidney disease (CKD) (stages 3–5)	Plasma (PL) sFas levels in patients with CKD were not significantly affected by the presence of carotid artery plaques (CAP). PL sFas levels in patients with CKD negatively correlated with estimated glomerular filtration rate (eGFR), but positively correlated with PL levels of some uremic toxins such as indoxyl sulfate (IS) and para-cresyl sulfate (p-CS), and some inflammatory biomarkers including sCD36, soluble receptor for advanced glycation end products (sRAGE), and fractalkine (FK). PL sFas levels were an independent predictor of mortality in patients with CKD.	P: 67 (total CKD), 20 [with CAP (CAP)], 44 (non-AP), disease severity in KDIGO classification: 7 (stage 1) [3 m/4 f; (Mn: 45, SD: 16.7)], 15 (stage 2) [4 m/8 f; (54, 11.2)], 20 (stage 3) [6 m/14 f; (61, 11.2)], 16 (stage 4) [9 m/7 f; (56, 14.9)], 9 (stage 5) [4 m/5 f; (61, 8.7)],	PL (sFas, pg/ml), ELISA (Mn, SD): [total CKD (1339, 659)], [CKD: CAP (1224.0, 584.7), non-CAP (1418.8, 694.8)]; $p = 0.289$ (CKD: CAP vs non-CAP), Corr. (vs sFas): $p < 0.001$, $r = -0.49$ (eGFR), $p = 0.001$, $r = 0.41$ (IS), $p < 0.001$, $r = 0.46$ (p-CS), $p < 0.001$, $r = 0.47$ (sCD36), $p = 0.001$, $r = 0.39$ (sRAGE), $p < 0.001$, $r = 0.43$ (FK), risk analysis for mortality (highest sFas): $p = 0.001$, HR = 1.002 (95% CI: 1.003–1.40)	[197]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Renal system diseases (excluding transplantation)				
sFasL, autosomal dominant polycystic kidney disease (ADPKD)	Serum (SR) sFasL levels in patients with ADPKD with impaired renal function (IRF) were significantly higher than those in patients with preserved renal function (PRF) and healthy controls (HC). SR sFasL levels in patients with PRF were also significantly higher than those in HC, despite similar renal function. SR sFasL levels showed a strong negative correlation with renal function evaluated by the estimated glomerular filtration rate (eGFR).	P: 52 (total ADPKD), 26 (IRF: eGFR 45-70 ml/min 1.73 m^2) [13 m/13 f; (Mn: 44.0, SD: 12.1)], 26 (PRF: eGFR > 70) [13 m/13 f; (43.0, 1.2)], C: 26 (HC) [13 m/13 f; (43.5, 11.2)]	SR (sFasL, ng/ml), ELISA (Mn, SD): [ADPKD: IRF (13.12, 1.69), PRF (9.6, 1.28)], [HC (6.59, 1.17)]; $p < 0.001$ (ADPKD: IRF vs PRF; ADPKD: IRF, PRF vs HC), Corr. (vs sFasL): $p < 0.001$, $r = -0.799$ (eGFR)	[198]
sFas, severe acute kidney injury (AKI) with Kidney Disease Improving Global Outcomes stage 2 and 3	Plasma (PL) sFas levels were a good candidate for variables in a model derivation (MD) cohort, but was not adopted as a final component in the developed three-variable model that predicted patients who progressed to severe AKI in the examination of internal validation (IV) and external validation (EV) cohorts.	P: 749 [MD cohort (MD)] [493 m/256 f; (Mn: 55, SD: 16)], 326 [IV cohort (IV)] [203 m/123 f; (55, 17)], 262 [EV cohort (EV)] [161 m/101 f; (63, 17)]	PL (sFas, pg/ml), MPAA, P (Md, Iqr): [MD (10780, 7958–15283)], [IV (10583, 7663–14721)], [EV (10310, 7230–14488)]; C statistic (sFas in MD) = 0.86 (95% CI: 0.80–0.91)	[199]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Renal system diseases (excluding transplantation)				
sFas, non-dialysis dependent chronic kidney disease (NDDCKD) with anemia (ANE)	Serum (SR) sFas levels in patients with NDDCKD with ANE requiring erythropoiesis-stimulating agent (ESA) therapy were significantly higher than those in patients who did not require ESA therapy. SR sFas levels showed a significant positive correlation with SR erythropoietin (EPO) levels, but a significant negative correlation with SR hemoglobin (Hb) levels and estimated glomerular filtration rate (eGFR). SR sFas levels may predict the necessity of ESA therapy in patients with NDDCKD.	P: 77 [total NDDCKD with ANE (NDDCKD-ANE)], 35 [requiring ESA therapy (ESA) [17 m/18 f; (Mn: 61, SD: 12)], 42 (non-ESA) [26 m/16 f; (56, 14)]	SR (sFas, pg/ml), ELISA (Mn, SD): [NDCKD-ANE: ESA (4316, 897), non-ESA (2776, 749)]; $p = 0.0001$ (NDCKD-ANE: ESA vs non-ESA), Corr. (vs sFas): $p = 0.001$, $r = 0.30$ (EPO), $p < 0.001$, $r = -0.55$ (Hb), $p < 0.001$, $r = -0.58$ (eGFR), risk analysis for ESA therapy (sFas): $p = 0.004$, OR = 1.012 (95% CI: 1.004–1.020)	[200]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Hepatic system diseases				
sFas and sFasL, nonalcoholic fatty liver disease (NAFLD) with/without nonalcoholic steatohepatitis (NASH)	Plasma (PL) sFas, but not sFasL, levels in patients with NASH were significantly higher than those in non-NASH cases. A model including PL sFas levels generated from the initial cohort (IC) worked well in the prediction of NASH presence in the validation cohort (VC), supporting the practical use of PL sFas levels as a clinical biomarker in noninvasive NASH diagnosis. Significant positive correlations were observed in IC between PL sFas levels and several liver histologic characteristics (LHC) related to NASH, including fibrosis (FB), lobular inflammation (LI), steatosis (ST), hepatocyte ballooning (HB), and the NAFLD activity score (NAS).	[IC] 95 [total liver biopsy (LB)] [48 m/47 f; (Mn: 50, SD: 11.6)], P: 41 (NASH) [17 m/24 f; (52.8, 10.1)], C: 54 (non-NASH) [31 m/21 f; (47.8, 12.3)], [VC] 82 (total LB) [66 m/16 f; (50.1, 9.8)], P: 20 (NASH) [16 m/4 f; (50.8, 10.2)], C: 62 (non-NASH) [50 m/12 f; (49.9, 9.7)]	PL (sFas/sFasL, sFas: ng/ml; sFasL: pg/ml), ELISA (Md, Iqr): [total IC-LB (7.6/78, 5.4–10.3/65–91)], [IC: NASH (11.8/80, 7.8–12.5/66–92), non-NASH (5.9/76, 4.8–8.3/65–85)], sFas: [VC: NASH (5.6, 4.5–6.2), non-NASH (4.1, 3.4–5.2)]; $p < 0.001/p = 0.2$ (IC: NASH vs non-NASH), sFas: $p = 0.004$ (VC: NASH vs non-NASH), risk analysis for NASH (IC: per 1 ng/ml increase in sFas): $p = 0.0004$, OR = 1.6 (95% CI: 1.2–2.06), Corr. (IC: vs sFas): $p < 0.001$ (all LHC below), r_s = [0.57 (95% CI: 0.40–0.74) (FB), 0.59 (0.42–0.75) (LI), 0.48 (0.30–0.66) (ST); 0.60 (HB) (0.43–0.76), 0.59 (0.42–0.76) (NAS)]	[201]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Hepatic system diseases				
sFas and sFasL, nonalcoholic fatty liver disease (NAFLD)	A decrease in plasma (PL) sFasL, but not sFas, levels after short-term aerobic exercise (AE) achieved a statistically near, but non-significant value in patients with NAFLD (>5% intrahepatic lipid). A significant correlation between reduction (Δ) in PL sFasL level and Δ in whole body fat oxidation (WB-FOX) after AE was observed in patients with NAFLD.	P: 13 (total NAFLD) [nd/nd; (Mn: 58, SEM: 3)], measurement time-points: before (BE) and after (AF) 7 consecutive days of AE	PL (sFas/sFasL, pg/ml), ELISA (Mn, SEM): [NAFLD-AE: BE (6483.2/66.5, 358.0/6.0), AF (6284.9/63.0, 315.7/5.7)]; p = ns/p = 0.06 (NAFLD-AE: BE vs AF), Corr.: $p < 0.05$, $r_s = -0.65$ (ΔsFasL vs ΔWB-FOX)	[202]
sFasL, nonalcoholic fatty liver disease (NAFLD) with/without hepatic fibrosis (FB) or nonalcoholic steatohepatitis (NASH)	Serum (SR) sFasL levels in patients with NAFLD with FB were significantly higher than those in patients without FB. However, SR sFasL levels could not discriminate advanced FB (AFB) from none to minimal FB (non-AFB). SR sFasL levels were not significantly affected by the presence of NASH. SR sFasL levels were identified as an independent predictor of FB in patients with NAFLD.	P: 37 (total NAFLD), 32 [with FB (FB)] [9 m/23 f; (Mn: 48, SD: 10)], 5 (non-FB) [3 m/2 f; (49, 11)]; FB status: 6 (AFB) [2 m/4 f; (51, 10)], 31 (non-AFB) [10 m/21 f; (48, 10)]; NASH status: 22 [with NASH (NASH)] [6 m/16 f; (49, 9)], 15 (non-NASH) [6 m/9 f; (47, 11)]	SR (sFasL, pg/ml), ELISA (Mn, SD): [NAFLD: FB (91, 30), non-FB (54, 26); adv-FB (86, 33), non-adv-FB (86, 33); NASH (89, 31), non-NASH (82, 34)]; p = 0.015 (NAFLD: FB vs non-FB), p = 0.805 (NAFLD: AFB vs non-AFB), p = 0.516 (NAFLD: NASH vs non-NASH), risk analysis for any FB in a prediction model (p = 0.0134): p = 0.0647, OR = 0.821 (95% CI: 0.665–1.012) (sFasL)	[203]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Hepatic system diseases				
sFas and sFasL, nonalcoholic fatty liver disease (NAFLD) with/without nonalcoholic steatohepatitis (NASH)	Serum (SR) sFas and sFasL levels in patients with NASH were significantly higher than those in patients with NAFLD without NASH (non-NASH) and healthy controls (HC). Significantly positive correlations of SR sFas levels with lobular inflammation (LI), and hepatocytes ballooning (HB) as well as a significant positive correlation between SR sFasL levels and steatosis (ST) were observed. SR sFas levels could be used for the assessment of disease severity in patients with NAFLD.	P: 40 (NASH) [4 m/36 f; (Mn: 45, SD: 2.1)], 40 (non-NASH) [8 m/32 f; (43, 1.3)], C: 15 (HC) [7 m/8 f; (43, 2.6)]	SR (sFas/sFasL, sFas: ng/ml and sFasL: pg/ml), ELISA (Mn, SD): [NASH (13.1/143.2, 2.3/28.3)], [non-NASH (7.08/26.87, 1.8/16.45)], [HC (5.58/21.4, 1.46/10.96)]; p = 0.000/p = 0.000 (NASH vs non-NASH, HC), Corr. (vs sFas/sFasL): p = 0.017/p = 0.463, r = 0.528/r = 0.174 (LI), p = 0.05/p = 0.075, r = 0.628/r = 0.407 (HB), p = 0.203/p = 0.04, r = 0.297/r = 0.461 (ST)	[204]
sFas and sFasL, compensated liver cirrhosis (CLC) with portal hypertension (PH)	In patients with CLC with PH (CLC-PH) holding hepatic vein pressure gradient (HVPG) ≥6 mmHg, but without gastroesophageal varices, serum (SR) sFas, but not sFasL, levels significantly correlated with HVPG values. Blood tests, including SR sFas levels in patients with CLC-PH, could prevent unnecessary esophagogastroduodenoscopy.	P: 90 (CLC-PH) [64 m/26 f; (Mn: 50.5, SD: 9.7, Rg: 32–72)]	SR (sFas/sFasL, nd), MPAA (nd): [CLC-PH (nd)]; Corr. (vs sFas/sFasL): p = 0.0354/p = 0.0894 (HVPG)	[205]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Hepatic system diseases				
sFas and sFasL, nonalcoholic fatty liver disease (NAFLD) with/without nonalcoholic steatohepatitis (NASH) (pediatric)	Plasma (PL) sFas and sFasL levels in pediatric patients with NAFLD with NASH were significantly higher than those in patients without NASH. PL sFas and sFasL levels significantly correlated with some histological features of NAFLD, including lobular inflammation (LI), hepatocytes ballooning (HB), and portal inflammation (PI). PL sFasL levels were a novel biomarker for predicting NASH, and the predicting efficacy was improved by combining PL sFasL levels with other risk factors into the NASH apoptosis score (NAS).	P: 117 (total NAFLD) [78 m/39 f; (Mn: 12.2, SD: 2.9)], 68 [with NASH (NASH)] [48 m/20 f; (12.7, 3.0)], 49 (non-NASH) [30 m/19 f; (11.6, 2.8)]	PL (sFas/sFasL, pg/ml), ELISA (Mn, SD): [total NAFLD (647.6/281.6, 216.7/149.9)], [NAFLD: NASH (686.0/324.9, 186.5/146.5), non-NASH (594.2/221.4, 244.9/134.0)]; $p = 0.023/p < 0.001$ (NAFLD: NASH vs non-NASH), Corr. (vs sFas/sFasL): $p = 0.082/p = 0.023$, $r = 0.16/r = 0.21$ (LI); $p < 0.001/p < 0.001$, $r = 0.37/r = 0.48$ (HB); $p = 0.003/p = 0.003$, $r = 0.27/r = 0.27$ (PI); ROC curve analysis for NASH diagnosis: AUC = 0.714 (95% CI: 0.618–0.810) (sFasL), AUC = 0.78 (95% CI = 0.69–0.87) (NAS)	[206]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Hepatic system diseases				
sFasL, nonalcoholic fatty liver disease (NAFLD) with/without nonalcoholic steatohepatitis (NASH) (adult)	Plasma (PL) sFasL levels in adult patients with NAFLD with definite NASH (DEF-NASH) were lower than those in patients with borderline NASH (BOR-NASH) or without NASH (non-NASH), however, associations with histologic features including NASH stage (NS), fibrosis (FB), steatosis (ST), hepatocyte ballooning (HB), and lobular inflammation (LI), were not statistically significant.	P: 648 (total NAFLD) [248 m/400 f; (Mn: 47.7, SD: 12.2)], 376 (DEF-NASH) [126 m/250 f; (47.9, 12.3)], 272 (total BOR-NASH and non-NASH) [122 m/150 f; (47.5, 12.0)], 129 (BOR-NASH), 143 (non-NASH)	PL (sFasL, pg/ml), MPAA (Mn, SD): [total NAFLD (71.3, 38.5)], [NASH: DEF (69.5, 38.0), BOR or non (73.8, 39.1)]; risk analysis for severity or histologic features of NASH: p = 0.178, OR = 0.95 (NS), p = 0.436, OR = 0.97 (FB), p = 0.160, OR = 0.94 (ST), p = 0.499, OR = 0.97 (HB), p = 0.171, OR = 0.95 (LI)	[207]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Hepatic system diseases				
sFasL, nonalcoholic fatty liver disease (NAFLD) with/without nonalcoholic steatohepatitis (NASH) (pediatric)	Plasma (PL) sFasL levels in pediatric patients with NAFLD with definite NASH (DEF-NASH), tended to be lower than those in patients with milder NASH stages, borderline zone 1 and 3 (BOR1-, BOR3-NASH), and without NASH (non-NASH), however, the difference lacked statistical significance. Among five typical histologic disease-severity indicators in NASH, steatosis (ST) and portal inflammation (PI) grades were more significantly associated compared to hepatocellular ballooning (HB), lobular inflammation (LI), and fibrosis (FB) grades. Higher PL sFasL levels were associated with the patient group with NASH with higher (>33%) ST grades.	P: 235 (total NAFLD) [182 m/53 f; (Mn: 13.1, SD: 2.6)], 73 (DEF-NASH) [56 m/17 f; (13.5, 2.3)], 47 (BOR-3 NASH) [35 m/12 f; (13.6, 2.8)], 53 (BOR-1 NASH) [46 m/7 f; (11.8, 2.0)], 62 (non-NASH) [45 m/17 f; (13.6, 2.9)], histology: 159 [with any FB (FB)], 75 (non-FB); 66 [0–33% ST (LST)], 169 [>33 % ST (HST)]; 117 [with HB (HB)], 118 (non-HB); 213 [with mild/more than mild PI (PI)], 228 (non-PI); 125 [<2 foci LI) (LLI)], 110 [≥2 foci LI (HLI)]	PL (sFasL, pg/ml), MPAA (Mn, SD): [total NAFLD (107.6, 71.4)], [NASH: DEF-(102.1, 51.1), BOR3, BOR1, and non (110.2, 78.8); FB (108.4, 71.9), non-FB (105.8, 71.3); LST (96.1, 65.2), HST (111.9, 73.3); HB (101.2, 56.6), non-HB (114.1, 83.5); PI (109.28, 73.37), non-PI (91.45, 45.99); LLI (111.2, 67.9), HLI (103.6, 75.2)]; p = 0.36 (NASH: DEF vs BOR3, BOR1, non), p = 0.12 (LST vs HST), p = 0.12 (PI vs non-PI), p = 0.18 (HB vs non-HB), p = 0.43 (LLI vs HLI), p = 0.8 (FB vs non-FB), risk analysis for HST (per 0.5 SD change of sFasL): p = 0.33, OR = 1.09 (95% CI: 0.92–1.28)	[208]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Hepatic system diseases				
DcR3, acute-on-chronic liver failure (ACLF)	Serum (SR) DcR3 levels in patients with ACLF were significantly higher than those in patients with liver cirrhosis (non-ACLF). SR DcR3 levels in survived patients (SUV) were significantly higher than those in non-survived patients (non-SUV), only with a model for end-stage liver disease (MELD) score >20. A change (Δ) in DcR3 levels within the first week after hospital admission predicted the patients' survival better than that in MELD score. SR DcR3 levels were not associated with bacterial infection (BI) in patients with ACLF. Dynamic changes in SR DcR3 levels may be a predictive biomarker of the prognosis of patients with ACLF.	P: 76 (total ACLF) [60 m/16 f; (Mn: 47.49, SD: 15.24)], 38 (SUV) [32 m/ 6 f; (44.74, 13.25)], 38 (non-SUV) [28 m/10 f; (50.24, 16.72)], measurement time-points: on hospital admission (OA), after 7 days (7D); 35 (BI), 41 (non-BI); MELD score: nd [≥ 20 (HMS)], nd [< 20 (LMS)], C: 41 (non-ACLF) [30 m/11 f; (43.95, 14.90)]	SR (DcR3, ng/ml), ELISA (Md, Iqr/Mn, SD): [total ACLF (0.97, 0.17–2.32)], [non-ACLF (0.21, 0.11–0.49)], [ACLF: HMS (2.91, nd), LMS (1.06, nd); SUV-OA (1.80, 2.60), non-SUV-OA (1.27, 1.54); Δ (SUV: OA and 7D) (−0.45, 0.21), Δ (non-SUV: OA and 7D) (0.15, 0.20); BI (1.64, 2.04), non-BI (1.45, 1.65)]; $p < 0.001$ (total ACLF vs non-ACLF), p = ns (ACLF-OA: SUV vs non-SUV), ACLF: SUV vs non-SUV: $p = 0.015$ (HMS), $p = 0.426$ (LMS), $p = 0.651$ (ACLF: BI vs non-BI), ROC curve analysis for survival (ΔDcR3/ΔMELD): $p = 0.024$/$p = 0.245$, AUC = 0.709/AUC = 0.606 (95% CI: 0.533–0.886/0.423–0.788)	[209]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Respiratory system diseases				
sFas and sFasL, chronic obstructive pulmonary disease (COPD)	Plasma (PL) sFas, but not sFasL, levels in patients with severe COPD (SEV-COPD) receiving supplemental O_2 were significantly higher than those in patients with mild/moderate COPD (MIL/MOD-COPD) without O_2, other diseases controls (OD) with O_2, including patients with old tuberculosis (OTB), idiopathic pulmonary fibrosis (IPF), pneumoconiosis (PC), and healthy controls (HC). No significant difference in sFas levels was observed between patients with low C-reactive protein levels (CRP) and those with high CRP.	P: 39 (total COPD), 19 (SEV-COPD) [13 m/6 f; (Mn: 66, SEM: 2)], 20 (MIL/MOD-COPD) [14 m/6 f; (66, 3)], CRP levels: <1.0 mg/dl (L-CRP), >1.0 mg/dl (H-CRP), C: 20 (total OD) [14 m/6 f; (67, 3)], 12 (OTB), 6 (IPF), 2 (PC), 22 (HC) [15 m/ 7 f; (66, 1)]	PL (sFas/sFasL, ng/ml), ELISA (Mn, SEM): [SEV-COPD (4.8/0.58, 1.0/0.01)], [MIL/MOD-COPD (2.8/0.55, 0.2/0.02)], [total OD (2.6/0.54, 0.2/ 0.02)], [HC (2.6/0.56, 0.1/0.02)]; $p < 0.05$/p = ns (SEV-COPD vs MIL/MOD-COPD, total OD, HC), sFas (in SEV-COPD, MIL/MOD-COPD): p = ns (L-CRP vs H-CRP)	[210]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Respiratory system diseases				
sFas and sFasL, chronic obstructive pulmonary disease (COPD) with/without cachexia (CX)	Serum (SR) sFasL, but not sFas, levels in patients with COPD were significantly lower than those in healthy controls (HC). SR sFasL levels in patients with COPD with CX in terms of either low body-mass-index (BMI) (BMI-CX) or low percent body fat (%fat) (%F-CX) were significantly higher than those in patients without CX. SR sFasL levels in patients with COPD showed significant negative correlations with BMI and %fat.	P: 70 (total COPD) [all m; (Mn: 72.3, SD: 7.2)], 45 [CX in terms of low BMI (<20 kg/m^2) (BMI-CX)], 25 (BMI-non-CX); 34 [CX in terms of low %F (<20 %) (%F-CX)], 36 (%F-non-CX), C: 47 (HC) [all m; (71.8, 7.4)]	SR (sFas/sFasL, sFas: ng/ml; sFasL: pg/ml), ELISA (Mn, SD): [total COPD (2.33/46, 0.84/29)], [HC (2.13/55, 0.62/28)], sFasL: [COPD-BMI: CX (51, 33), non-CX (36, 15)], [COPD-%F: CX (55, 33), non-CX (37, 21)]; p = ns/p < 0.05 (total COPD vs HC), sFasL: p < 0.05 (COPD-BMI: CX vs non-CX), p < 0.01 (COPD-%F: CX vs non-CX), Corr.: (vs sFasL in total COPD): p < 0.05, r = −0.307 (BMI), p < 0.05, r = −0.283 (%fat)	[211]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Respiratory system diseases				
DcR3, acute respiratory distress syndrome (ARDS)	In the test cohort (TC), plasma (PL) DcR3 levels in non-survived patients on day 28 (non-SUV) after onset were significantly higher than those in survived patients (SUV), and the DcR3 levels were the only biomarker that discriminated between them at all time-points during the first week. Non-SUV had significantly higher PL DcR3 levels than SUV, regardless of the acute physiology and chronic health evaluation (APACHE) II scores. PL DcR3 levels in patients with ARDS significantly correlated with the occurrence of multiple-organ dysfunction events (MOD), including septic shock (SS), renal failure (RF), metabolic acidosis (MA), and coagulopathy (CO), within 7 days. The usefulness of the PL DcR3 levels for the prediction of mortality in patients with ARDS was reconfirmed in the validation cohort (VC).	[TC] P: 88 (total ARDS), 34 (SUV) [28 m/6 f; (Mn: 72.0, SD: 11.9)], 54 (non-SUV) [49 m/5 f; (76.4, 13.0)], DcR3 level (ng/ml): ≤3 (LDcR3), >3 (HDcR3); APACHE II score: ≤25 (LAPA), >25 (HAPA), measurement time-points: 1 day (1D), 4 days (4D), 7 days (7D) after ARDS onset, DcR3 level (pg/ml) for survival curve analysis [<1100 (LDc), 1100–5600 (MDc), >5600 (HDc)]: 22 (LDc), 44 (MDc), 22 (HDc), [VC] P: 59 (total ARDS), 33 (SUV) [23 m/10 f; (71.2, 15.4)], 26 (non-SUV) [12 m/14 f; (61.9, 19.0)], 16 (LDc), 33 (MDc), 10 (HDc)	PL (DcR3, ng/ml), ELISA (Md, Iqr) [TC-SUV: 1D (1229, 785–2075), 4D (803, 342–1080), 7D (621, 325–981)], [TC-non-SUV: 1D (3413, 2021–11266), 4D (2001, 828–3071), 7D (3132, 705–4972)]; $p = 0.001$/$p = 0.040$/$p = 0.002$ (TC-1D/4D/7D: SUV vs non-SUV), $p = 0.045$/$p = 0.025$ (TC: HAPA/LAPA, SUV vs non-SUV), MOD within 7 days: $p < 0.005$ [TC-1D/4D/7D: LDcR3 vs HDcR3 (SS, RF, MA); TC-1D: LDcR3 vs HDcR3 (CO)], $p < 0.05$ [TC-4D/7D: LDcR3 vs HDcR3 (CO)], log-rank test for survival (TC/VC): $p < 0.0001$/$p = 0.028$ (among HDc, MDc, LDc), $p = 0.003$/$p = 0.268$ (HDc vs MDc), $p < 0.001$/$p = 0.01$ (HDc vs LDc), $p = 0.034$/$p = 0.034$ (MDc vs LDc)	[212]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Respiratory system diseases				
sFas, chronic obstructive pulmonary disease (COPD) with emphysema (EM)	Plasma (PL) sFas levels were examined in a test cohort (TC) of patients with COPD. PL sFas levels were identified as an independent biomarker significantly associated with radiologically-diagnosed EM, which was judged by % low attenuation area (%LAA) ≤ −910 Hounsfield units (HU) and mean lung attenuation at the 15th percentile on the lung attenuation curve (LP15A).	P: 341 (COPD in TC) [178 m/163 f; (Mn: 65, SD: 0.5)], 388 [COPD in validation cohort (VC)] [267 m/121 f; (66.6, 0.4)], C: 247 (non-COPD in TC) [124 m/123 f; (61, 3)]	PL (sFas, ng/ml), MPAA, P (Md, Iqr) [TC-COPD (15, 11–20)], multiple regression analysis for EM outcomes (sFas): $p = 0.016$, $\beta = 1.16$ (%LAA ≤ −910 HU), $p = 0.014$, $\beta = -8.53$ (LP15A)	[213]
sFasL, acute respiratory distress syndrome (ARDS)	Mean plasma (PL), but not bronchoalveolar fluid (BALF), sFasL levels in patients with ARDS decreased during the follow-up period in a phase II randomized controlled trial (RCT). A few-fold decrease in mean BALF sFasL levels compared to those in a previous study was found, which may reflect improvements in intensive care unit for patients with ARDS.	P: 90 (ARDS) [57 m/33 f; (Mn: 49.9, SD: 16.4)], measurement time-points: entry time (BS, n = 89), on 4 ± 1 days (4D, n = 66), 8 ± 1 days (8D, n = 42) in RCT	BALF and PL (sFasL, pg/ml, BALF/PL), ELISA (Mn, SD): [ARDS: BS (39.3/129.1, 2.0/381.2), 4D (40.1/60.2, 5.7/31.1), 8D (40.1/56.2, 4.7/28.9)], BALF: [BS in a prior study conducted in 1999 (Mn: ~150)]	[214]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Respiratory system diseases				
sFas and sFasL, pulmonary thromboembolism (PTE) (acute)	Serum (SR) sFas, but not sFasL, levels in patients with acute PTE were significantly higher than those in healthy controls (HC). Also, SR sFas, but not sFasL, levels in survived patients (SUV) with PTE were significantly lower than those in non-survived patients (non-SUV). SR sFas levels can be used as an auxiliary diagnostic and prognostic biomarker.	P: 45 (total PTE) [26 m/19 f; (Mn: 68.17, SD: 16.9)], 38 (SUV), 7 (non-SUV), C: 40 (HC) [24 m/16 f; (66.33, 17.5)]	SR (sFas/sFasL, pg/ml), ELISA (Mn, SD): [total PTE (509.1/139.9, 67.6/23.7)], [HC (332.1/130.4, 28.0/34.6)], [PTE: SUV (491.5/140.7, 58.5/26.3), non-SUV (595.2/138.3, 36.7/5.8)]; $p = 0.001$/$p = 0.19$ (total PTE vs HC), $p < 0.001$/$p = 0.817$ (PTE: SUV vs non-SUV)	[215]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Respiratory system diseases				
DcR3, chronic obstructive pulmonary disease (COPD)	Serum (SR) DcR3 levels in male patients with COPD were significantly higher than those in healthy controls (HC), and the levels were more elevated in acute exacerbation (AE) phase or advanced disease stages (DS) compared to those in stable phase (ST) or milder DS. SR DcR3 levels were significantly correlated with several parameters suggesting a reduced quality of life and increased severity of hypoxia, including predicted forced expiratory volume in 1 second (pFEV1%), predicted forced vital capacity (pFVC%), dyspnea (DYS), the global initiative for chronic obstructive lung disease (GOLD) stage, COPD assessment test score (CAT), smoking history per year (SH), and peripheral O_2 saturation (SpO_2).	P: 30 (total AE-COPD) [all m; (Mn: 59.77, SD: 6.66)], 8 (GOLD I-II) [all m; (60.50, 11.60)], 22 (GOLD III-IV) [all m; (59.50, 4.02)], 30 (total ST-COPD) [all m; (58.23, 9.06)], DS: 14 [GOLD stage I-II (GOLD I-II)] [all m; (57.21, 9.20)], 16 (GOLD III-IV) [all m; (59.12, 9.14)], C: 30 (HC) [all m; (56.03, 8.16)]	SR (DcR3, ng/ml), ELISA; P (Md, Iqr): [total AE-COPD (4.5, 4–12)], [total ST-COPD (3, 3–5)], [HC (3, 2–4)], [AE-COPD-GOLD: I-II (4, 2–4), III-IV (6.50, 4–13)], [ST-COPD-GOLD: I-II (3, 3–3), III-IV (4.50, 3–8.50)]; $p < 0.001$ (total AE-COPD vs HC; AE-COPD-GOLD: I-II vs III-IV), $p < 0.05$ (total ST-COPD vs HC; COPD-GOLD III-IV: ST vs AE), $p < 0.01$ (total-COPD: ST vs AE; ST-COPD-GOLD: I-II vs III-IV), p = ns (COPD-GOLD I-II: ST vs AE), Corr. (vs DcR3): $p < 0.001$, r = [−0.671 (pFEV1%), −0.617 (pFVC%), 0.658 (GOLD), 0.561 (DYS), 0.553 (CAT), 0.476 (SH)], $p < 0.05$, r = −0.461 (SpO_2)	[216]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
4. Central nervous system diseases				
sFas and sFasL, post-hemorrhagic (PH)/non-hemorrhagic (NH) hydrocephalus (HDC) in very low birth-weight (VLBW) infants	Cerebrospinal fluid (CSF) sFas levels in infants with VLBW with either PH-HDC or NH-HDC were much higher than those in non-HDC controls. No significant difference in CSF sFas levels was observed between the samples from patients with PH-HDC and those from patients with NH-HDC. CSF sFas levels in patients with PH-HDC with peri-ventricular leukomalacia (PVL) were significantly higher than those without PVL. CSF sFasL levels in all samples were below the detection limit.	P: 15 (total PH-HDC) [8 m/7 f; (gestational age: Md: 25 weeks+3 days, Rg: 23 weeks+3 days–3 weeks+4 days)], 8 [with PVL (PVL)], 7 (non-PVL), 7 (NH-HDC) [nd/nd, (nd)], C: 24 (total non-HDC), 11 (pre-term) [nd/nd; (27 weeks+5 days, 15 weeks+5 days–32 weeks+5 days)], 13 (term or near-term) [nd/nd; (38 weeks, 32–40 weeks)]	CSF (PH/NH-HDC: ventricular; non-HDC: lumber, sFas and sFasL, ng/ml), ELISA (Md, Rg): sFas: [PH-HDC (131, 51–279) in 3 samples], [NH-HDC (127, 35–165)], [non-HDC: (24, 20–43) in 9 cases, (<0.5 ng/ml) in 15 cases], [PH-HDC: PVL (164, 76–227), non-PVL (nd, ca. 62–ca. 150)], sFasL: [all cases (<0.5 ng/ml)]; sFas: p = 0.09 (HDC: PH vs NH), p = 0.014 [PH-HDC: PVL vs non-PVL]	[217]
sFasL, high-pressure hydrocephalus (HP-HDC) (neonatal)	Cerebrospinal fluid (CSF) sFasL levels in neonatal patients with HP-HDC caused by spina bifida aperta (SBA), aqueduct stenosis (AS), or fatal intra-cerebral hemorrhage (FICH) were unchanged from those in healthy controls (HC).	P: 30 (total HP-HDC) [nd/nd; (gestational ages, Rg: 27–54 weeks)], (20 SBA, 4 AS, 6 FICH), C: 15 (HC) [nd/nd; (gestational ages, 24–54 weeks)]	CSF (sFasL, ng/ml), ELISA (Rg): [HP-HDC by SBA, AS, or FICH (all groups <0.5)], C: [HC (<0.5)]	[218]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
4. Central nervous system diseases				
sFas, Alzheimer's disease (AD) [mild dementia, mild cognitive impairment (MCI), pre-MCI]	Cerebrospinal fluid (CSF) sFas levels in patients with very mildly or mildly demented AD defined by the Clinical Dementia Rating scale (CDR) were significantly higher than those in non-AD controls. CSF sFas levels in patients with AD significantly correlated with the best-performing traditional CSF marker, tau protein/amyloid-β peptide 1–42 ratio (T/AB), and the levels were identified as a biomarker that enhanced the ability of T/AB in the diagnosis of AD.	P: 91 (total AD), 28 (CDR 1) [14 m/14 f; (Rg: >60)], 63 (CDR 0.5) [33 m/30 f; (>60)], C: 242 [non-AD: (CDR 0)] [157 m/85 f; (>60)]	CSF (log sFas, ng/ml), MPAA (Mn, SD): [total AD (−0.173, 0.133)], [non-AD (−0.252, 0.123)]; $p = 0.0002$ (total AD vs non-AD), Corr. (vs sFas): $p < 0.0001$, $r = 0.288$ (T/AB), ROC analysis for AD diagnosis: AUC = 0.8518 (log sFas and log T/AB combined), AUC = 0.8443 (log T/AB alone)	[219]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
4. Central nervous system diseases				
sFasL, hypoxic-ischemic encephalopathy (HIE) (infant)	Cerebrospinal fluid (CSF) sFasL levels in term infant patients with HIE with moderate (HIE-II) and severe (HIE-III) grades were significantly higher than those with mild (HIE-I) grade and healthy controls (HC). CSF sFasL levels in infant patients with HIE were significantly correlated with both a predictor of neurological outcomes, Apgar score at 10 min (AP10), and HIE-grade (HIEG). CSF sFasL levels alone or in combination with interleukin (IL)-6 levels predicted adverse outcomes at 18 months in asphyxiated infants equally or better than the standard biomarker, cord blood pH (CBpH).	P: 44 (total HIE), 14 (HIE-I) [7 m/7 f; (gestational age: Md: 41.1 weeks, Iqr: 37.4–41.3 weeks)], 16 (HIE-II) [9 m/7 f; (40.1 weeks, 38.6–40.3 weeks)], 14 (HIE-III) [6 m/8 f; (39.0 weeks, 37.2–40.4 weeks)], outcomes at 18 months: 24 [adverse (ADV-OC)], 20 [normal (NOR-OC)], C: 20 (HC) [10 m/10 f; (39.5 weeks, 38.8–41.7 weeks)]	CSF (sFasL, pg/ml), ELISA (Md, Iqr): [total HIE (62, 16–119)], [HIE-I (10.6, 0–41.6), HIE-II (75.7, 43.7–129.4), HIE-III (105.2, 28.5–168.6)], [HC (0, 0–0)]; $p < 0.0001$ (total HIE vs HC; HIE-II, HIE-III vs HIE-I, HC), Corr. (vs sFasL): $p < 0.0001$, $r_s = -0.577$ (AP10), $p < 0.0001$, $r_s = 0.6898$ (HIEG), ROC curve analysis for prediction of ADV-OC: $p < 0.0001$, AUC = 0.855 (sFasL alone); $p < 0.0001$, AUC = 0.939 (sFasL and IL-6 combined), AUC = 0.86 (CBpH)	[220]
sFas, traumatic brain injury (TBI) (severe)	Cerebrospinal fluid (CSF) sFas levels in patients with severe (Glasgow Coma Scale ≤8 and a positive cranial CT scan) TBI (SEV-TBI) were significantly higher than those in healthy controls (HC).	P: 45 (SEV-TBI) [33 m/12 f; (Mn: 32.7, SD: 15.0)], C: 25 (HC) [18 m/7 f; (30.1, 13.0)]	CSF (sFas, ng/ml), ELISA (Mn, SD): [SEV-TBI (169.1, 12.3)], [HC (15.3, 3.0)]; $p < 0.05$ (TBI vs HC)	[221]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
5. Endocrine system diseases				
sFas and sFasL, Type 1 diabetes mellitus (T1DM) with albumin urea (AU)	Serum (SR) sFas, but not sFasL, levels in patients with T1DM with normo-albumin urea (NAU) were significantly lower than those in patients with micro-albumin urea (MAU). SR sFas levels were significantly correlated with cystatin-C based estimated glomerular filtration rate (cC-GFR) after adjustment for age, median albumin excretion rate in urea (AER), and soluble tumor necrosis factor receptor (sTNFR)1 level. SR sFas levels were strongly associated with renal- function decline in patients with T1DM.	P: 667 (total T1DM), [363 [total normo-AU (NAU)] [160 m/203 f; (Mn: 39, SD: 12)], 183 [cC-GFR >115 (G1)] [nd/nd; (37, 11)], 180 [cC-GFR <115 (G2)] [nd/nd; (40, 13)], 304 [total micro-AU (MAU)] [185 m/119 f; (41, 12)], 152 [cC-GFR >101 (G3)] [nd/nd; (36, 12)], 152 [cC-GFR <101 (G4)] [nd/nd; (45, 11)]	SR (sFas/sFasL, sFas: ng/ml; sFasL: pg/ml), MPAA (Md, Iqr): [T1DM-NAU: G1 (3.8/0.12, 3.0–4.7/0.08–0.19), G2 (4.5/0.13, 3.7–5.5/0.07–0.20)], [T1DM-MAU: G3 (4.5/0.12, 3.6–5.6/0.08–0.18), G4 (5.4/0.11, 3.7–6.9/0.06–0.16)]; $p < 0.0001$/p = ns (T1DM: total NAU vs total MAU; T1DM: among G1, G2, G3, G4), Corr. (sFas at 25th 50th, and 75th percentile vs mean cC-GFR): $p < 0.008$, $r^2 = 0.45$ (adjusted for age, AER, sTNFR1)	[222]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
5. Endocrine system diseases				
sFas and sFasL, type 2 diabetes mellitus (T2DM) with/without diabetic foot lesions (DFL)	Both serum (SR) sFas and sFasL levels in patients with T2DM with diabetic foot lesions (DFL) were significantly higher than those in patients without DFL and healthy controls (HC). SR sFas, but not sFasL, levels in patients with T2DM without DFL were significantly higher than those in HC. A significant positive correlation with high-sensitive C-reactive protein (hs-CRP) was observed for SR sFas and sFasL levels in patients with T2DM with DFL. SR sFas and sFasL levels may be help in the early diagnosis and management of patients with T2DM with DFL.	P: 50 (total T2DM), 25 [with DFL (DFL)] [nd/nd; (Mn: 58.12, SD: 9.29)], 25 (non-DFL) [nd/nd; (59.60, 9.27)], C: 30 (HC) [nd/nd; (53.13, 8.61)]	SR (sFas/sFasL, ng/ml), ELISA (Mn, SD): [T2DM: DFL (12.20/2.55, 2.18/1.06), non-DFL (10.55/1.75, 2.57/0.62)], [HC (5.91/1.59, 3.10/0.32)]; p = 0.0001/p = 0.028 (among T2DM-DFL, T2DM-non-DFL, HC), p = 0.019/p = 0.036 (T2DM: DFL vs non-DFL), p = 0.0001/p = 0.014 (T2DM-DFL vs HC), p = 0.0001/p = 0.244 (T2DM-non-DFL vs HC), Corr. (vs sFas/sFasL, in T2DM-DFL): p = 0.032/p = 0.018, r = 0.429/r = 0.471 (hs-CRP)	[223]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
5. Endocrine system diseases				
sFas and sFasL, type 2 diabetes mellitus (T2DM) with/without arterial hypertension (AH)	Serum (SR) sFasL, but not sFas, levels in patients with T2DM irrespective of the presence of AH were significantly lower than those in healthy controls (HC). SR sFasL levels in patients with T2DM decreased in subjects with impairment of glucose tolerance and presence of AH. Patients with pre-T2DM without AH had intermediate SR sFasL values between those of patients with T2-DM without AH and HC.	P: 105 (total T2DM), 19 [with drug-controlled AH (DCAH)] [11 m/8 f; (Mn: 48.11, SD: 7.64)], 30 [with drug-naïve AH (DNAH)] [20 m/10 f; (47.40, 11.88)], 30 [without AH (non-AH)] [14 m/16 f; (47.57, 8.62)], 26 [preT2DM without AH (P-non-AH)] [8 m/18 f; (45.15, 13.41)], C: 19 (HC) [10 m/9 f; (42.42, 10.64)]	SR (sFas/sFasL, pg/ml), ELISA (Mn, SD): [T2DM: DCAH (ca. 6900/ca. 44, ca. 1600/ca. 17), DNAH (ca. 7000/ca. 54, ca. 1400/ca. 26), non-AH (ca. 7300/ca. 67, ca. 2400/ca. 34), P-non-AH (ca. 8100/ca. 71, ca. 1600/ca. 38)], [HC (ca. 7500/ca. 89, ca. 2000/ca. 33)]; p = ns/p < 0.001 (T2DM: DCAH vs HC), p = ns/p < 0.05 (T2DM-non-AH vs HC)	[224]
sFas, type-2 diabetes mellitus (T2DM) with/without cardiovascular diseases (CVD)	Non-DM patients with cardiovascular disease (CVD) had significantly higher baseline plasma (PL) sFas levels than those in patients without CVD, however, no significant difference was observed in the patients with T2DM. Development of DM incidence was significantly increased in patients with the highest tertile of PL sFas levels, and these patients had a significantly increased risk of developing T2DM events.	P: 363 (total T2DM), 95 [with CVD (CVD)] [58 m/37 f; (Mn: 61, SD: 4.77)], 268 (non-CVD) [147 m/121 f; (58.57, 5.79)], C: 4379 (total non-DM), 532 (CVD) [291 m/241 f; (60.27, 5.30)], 3847 (non-CVD) [1399 m/2448 f; (56.95, 5.9)]	PL (sFas, arbitrary units), MPAA (PEA) (Mn, SD): [T2DM: CVD (189, 63), non-CVD (185, 79)], [non-DM: CVD (177, 67), non-CVD (166, 93)]; p < 0.0001 (non-DM: CVD vs non-CVD), p = ns (T2DM: CVD vs non-CVD), risk analysis for T2DM development (highest sFas tertile, adjusted for age and gender): p = 0.001, HR = 1.36 (95% CI: 1.13–1.65), log-rank test for cumulative DM-free survival: p < 0.0001 (among sFas tertiles)	[183]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
5. Endocrine system diseases				
sFasL, type 2 diabetes mellitus (T2DM) with macular edema (ME)	Baseline aqueous eye humor (AEH) sFasL levels in patients with T2DM with ME were significantly higher than those in healthy controls (HC). AEH sFasL levels in patients with T2DM with ME significantly decreased after subthreshold micropulse laser (SML) treatment. AEH sFasL levels may contribute to the management of ME in patients with T2DM as a potent biomarker.	P: 18 [T2DM with ME (T2DM-ME)] [10 m/8 f; (Mn: 63, SD: 8.7)], measurement time-points: at baseline (BS), 1 month (1M), 3 months (3M), 12 months (12M) after SML treatment, C: (HC) [6 m/4 f; (69, 9.8)]	AEH (sFasL, arbitrary units), MPAA (Mn, SD): [T2DM-ME-SML: BS (124.9, 76.0), 1M (58.7, 14.2), 3M (85.5, 40.5), 12M (76.6, 39.2)], [HC-BS (71.6, 116.2)]; $p = 0.041$ (BS: T2DM-ME vs HC), $p = 0.0098$ (T2DM-ME: BS vs 1M)	[225]
6. Dermal system diseases				
sFasL, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)	Serum (SR) sFasL levels in patients with TEN and SJS at the beginning phase were significantly higher than those in patients with ordinary erythema multiforme-type drug eruption (EMDE) or healthy controls (HC). SR sFasL levels in patients with TEN and SJS decreased significantly within 3 to 6 days after onset of the diseases. SR sFasL levels may be a good biomarker for the early diagnosis of TEN and SJS.	P: 8 (TEN) [3 m/5 f; (Mn: 42, SD: 20)], 14 (SJS) [6 m/8 f; (37, 15)], measurement time-points (TEN/SJS, n = 6): at disease onset (0D), after 3-6 days (3/6D), C: 14 (EMDE) [8 m/6 f; (40, 10)], 14 (HC) [8 m/6 f; (43, 17)]	SR (sFasL, pg/ml), ELISA (Mn, SD): [TEN (131.5, 57.4)], [SJS (119.1, 41.0)], [EMDE (42.1, 3.5)], [HC (<40, nd)], [TEN/SJS: 0D (105.5, 25.4), 3/6D (46.7, 10.4)]; $p < 0.0001$ (TEN, SJS vs EMDE, HC), $p < 0.01$ (TEN/SJS: 0D vs 3/6D)	[226]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
6. Dermal system diseases				
sFas and sFasL, maculopapular rash (MPR), erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)	Serum (SR) sFas and sFasL levels in patients with all drug/virus-induced skin eruptions (D/V-SE) and some other dermal diseases were elevated as compared to healthy controls (HC). SR sFasL levels in patients with MPR at disease onset were highly elevated, but decreased to a negative level after 3 days. SR sFasL levels in patients with acute viral exanthemas (AVE), others with inflammatory diseases excluding atopic/contact dermatitis, autoimmune diseases, and HC were negative. SR sFasL levels may be a biomarker for the discrimination between drug rashes and VE.	P: 51 (total D/V-SE) [23 m/28 f; (nd)], 42 (generalized MPR), 3 (herpes-simplex-triggered EM), 2 (SJS), 4 (TEN), measurement time-points (MPR): at disease onset (0D), after 3 days (3D), C: 160 (total non-MPR) [77 m/83 f; (nd)], 26 (VE), 134 other inflammatory diseases, 142 (HC), P and C (except HC): (Rg: 12–94)	SR (sFas/sFasL, ng/ml), ELISA (Rg): [MPR: (0.36–1.19/0.67–6.95 (0D), negative (3D))], [EM (0.13–0.32/0.61–0.75)], [SJS (0.39–1.29/3.16–3.83)], [TEN (0.52–0.92/0.16–0.58)], [HC (negative/negative)], [AVE (0–0.93/negative)], [atopic dermatitis (0–1.60/0–1.89)], [contact dermatitis (nd/0–1.49)], [cellulitis (0–1.25/negative)], [systemic lupus erythematosus (0–1.10/negative)], [psoriasis (0.14–1.33/negative)]	[227]
sFasL, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)	Blister fluid (BF) sFasL levels in patients with SJS/TEN, burn injuries (BI), bullous pemphigoid (BP), and serum (SR) sFasL levels in healthy controls (HC) were examined in a Figure, however, no detailed information about differences among their sFasL levels was provided.	P: 29 (SJS/TEN) [nd/nd; (nd)], C: 15 (BI) [nd/nd; (nd)], 5 (BP) [nd/nd; (nd)], 13 (HC) [nd/nd; (nd)]	BF and SR (for HC) (sFasL, ng/ml), ELISA (Mn, SD): [SJS-TEN (0.41, 0.5)], [BI, BP, HC (nd, nd)]	[228]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
6. Dermal system diseases				
sFasL, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)	Serum (SR) sFasL levels in most patients with SJS/TEN significantly increased to peak concentrations a few days before the onset of skin detachment and mucosal lesions. Elevated SR sFasL levels decreased rapidly within 5 days after disease onset to those in patients with ordinary types of drug-induced skin reaction (ODSR) and healthy controls (HC). SR sFasL levels might be a useful biomarker for early-phase diagnosis of drug-induced skin reactions in SJS/TEN patients.	P: 35 (total SJS/TEN), 19 (SJS) [10 m/9 f: (Mn: 44.8, SD: 25.0)], 16 (TEN) [10 m/6 f; (47.9, 23.4)], measurement time-points (in terms of disease onset): −4 to −2 days (−4/−2D), −1 to 2 days (−1/2D), 3 to 5 days (3/5D), 6 to 10 days (6/10D), ≥11 days (11D), C: 32 (ODSR) [10 m/22 f; (50.4, 21.8)], 33 (HC) [19 m/14 f; (29.9, 3.1)]	SR (sFasL, pg/ml), ELISA (Mn, SD): [SJS/TEN: −4/−2D (147.76, 104.4), −1/2D (68.8, 33.4), 3/5D (45.3, 11.9)], [ODSR (45.0, 11.1)], [HC (42.8, 8.2)]; $p = 0.020$ [SJS/TEN-(−4/−2D) vs ODSR], $p = 0.019$ [SJS/TEN-(−4/−2D) vs HC], $p < 0.05$ (SJS/TEN: −4/−2D vs −1/2D), $p = 0.19$ (ODSR vs HC)	[229]
7. Obstetric system diseases				
sFasL, intrauterine growth restriction (IUGR)	No significant difference in either maternal blood (MBL)-serum (SR) or umbilical cord blood (UCBL)-SR sFasL levels was observed between the samples from patients with IUGR and those from non-IUGR controls. MBL-SR sFasL levels weakly correlated with UCBL-SR sFasL levels in non-IUGR controls, but not those in patients with IUGR.	P: 80 (IUGR) [all f; (Mn: 28.3, SD: 6.2)], C: 79 (non-IUGR) [all f; (31.6, 6.2)]	SR (MBL and UCBL) (sFasL, pg/ml), ELISA (nd); p = ns (MBL/UCBL: IUGR vs non-IUGR), Corr. (vs sFasL): $p < 0.05$, $r = 0.35$ (non-IUGR: MBL vs UCBL), $p > 0.05$, $r = 0.05$ (IUGR: MBL vs UCBL)	[230]

Continued on next page

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
7. Obstetric system diseases				
DcR3, preeclampsia (PE)	Plasma (PL) DcR3 levels in patients with PE at the 3rd pregnancy trimester (3PT) were significantly lower than those in healthy controls (HC) at 3PT. Decreased PL DcR3 levels may be related to the onset of PE.	P: 10 [PE at 3PT (PE-3T)] [all f; (Mn: 33.1, SD: 3.1)], C: 36 (HC) [all f; (33.1, 3.6)]	PL (DcR3, pg/ml), ELISA (Mn, SD): [PE-3PT (ca. 300, ca. 120)], [HC-3PT (ca. 670, ca. 150)]; p = 0.015 (3PT: PE vs HC)	[231]

PL sFas levels in patients with critically ill acute kidney injury (AKI) exhibiting a nonresolving subphenotype (non-RS) were significantly higher than those in patients exhibiting a resolving subphenotype and non-AKI controls [196]. PL sFas levels were the only biomarker significantly associated with non-RS after adjustment for major risk factors such as age, body mass index (BMI), DM, and APACHE III score [196]; however, the level was not adopted as a final component in a three-variable model for the prediction of patients who progressed to severe AKI [199]. SR sFasL levels in patients with autosomal dominant polycystic kidney disease (ADPKD), accompanied by impaired renal function, were significantly higher than those in patients with preserved renal function (PRF) [198]. SR sFasL levels in patients with ADPKD with PRF were still elevated compared with those in healthy controls, and the SR sFasL levels showed a strong negative correlation with eGFR.

3.5.2. Hepatic system diseases [201–209]

PL/SR sFas and sFasL levels in patients with nonalcoholic fatty liver disease (NAFLD) have been repeatedly investigated to identify the presence of nonalcoholic steatohepatitis (NASH). The sFas in patients with NAFLD with NASH consistently presented significantly higher levels than those in patients without NASH and healthy controls [201,204,206], with varying statistical significant differences in the sFasL levels between NASH cases and non-NASH cases [201,204,207,208]. sFas and/or sFasL levels often presented significant positive correlations with several liver histologic characteristics, including LF, lobular inflammation, steatosis, and hepatocyte ballooning, which are useful for the assessment of NAFLD severity [201,203,204,206]. Changes in PL sFasL levels in patients with NAFLD after short-term aerobic exercise were significantly correlated with changes in whole-body fat oxidation [202].

Significantly elevated levels of SR sFas, but not of SR sFasL, were observed in patients with compensated liver cirrhosis accompanied by portal hypertension (CLC-PH) with a hepatic vein pressure gradient higher than 6 mmHg, but lacking gastroesophageal varices [205]. Evaluation of SR sFas levels in patients with CLC-PH may prevent unnecessary esophagogastroduodenoscopy. SR DcR3 levels in patients with acute-on-chronic liver failure (ACLF) were significantly higher than those in non-ACLF controls [209]. Dynamic changes in DcR3 levels within the first week after hospital admission, rather than those at the time of hospital admission, better predicted the prognosis of ACLF, as compared to the commonly used model for end-stage liver disease (MELD) score.

3.5.3. Respiratory system diseases [210–216]

PL sFas, but not sFasL, levels in patients with severe chronic obstructive pulmonary disease (COPD) receiving supplemental oxygen gas treatment (O_2T) were significantly higher than those in patients with mild/moderate COPD without O_2T, non-COPD disease-patient controls with O_2T, and healthy controls; however, significantly higher sFas levels were not observed in patients with either severe or mild/moderate COPD with elevated CRP levels [210]. SR sFasL, but not sFas, levels in patients with COPD, especially in non-cachexic patients in terms of either low BMI or low percent body fat (%fat) levels, were significantly lower than those in healthy controls [211]. The SR sFasL levels showed a significant negative correlation with BMI and %fat level. SR DcR3 levels in male patients with COPD were higher than those in healthy controls [216]. The SR DcR3 levels were significantly elevated in patients in the acute exacerbation phase or advanced disease stages, as

assessed by clinical COPD evaluation criteria, in comparison with those in the stable phase or milder disease stages and presented significant positive correlations with several clinical parameters, showing both reduced quality of life and increased severity of hypoxia. In addition,, PL sFas levels in patients with COPD were significantly associated with the severity indices of radiologic emphysema diagnosed using computed tomography [213].

PL DcR3 levels in patients with non-surviving acute respiratory distress syndrome (ARDS) on day 28 after onset were significantly higher than those in the surviving patients, and the DcR3 levels were the only biomarker that discriminated them at all time-points in the first week after onset [212]. The DcR3 levels in the non-surviving patients were significantly higher, regardless of the APACHE II scores. The usefulness of the DcR3 level as a predictive biomarker for mortality in patients with ARDS was suggested by the significant associations of DcR3 levels in patients with ARDS with the occurrence of multiple organ dysfunction events, including septic shock, renal failure, metabolic acidosis, and coagulopathy, within 7 days after onset. PL, but not bronchoalveolar, sFasL levels in patients with ARDS exhibited a large decrease during the 8 days follow-up period after onset [214]. SR sFas, but not sFasL, levels in acute pulmonary thromboembolism (PTE) patients were significantly higher than those in healthy controls [215]. The sFas levels in non-surviving patients with PTE were significantly elevated compared with those in surviving patients, suggesting that sFas levels could be used as an auxiliary diagnostic and prognostic biomarker in PTE.

3.5.4. Central nervous system diseases [217–221]

CSF sFas and sFasL levels have been examined to determine their potential as clinical biomarkers for several central nervous system diseases. CSF sFas, but not sFasL, levels in infants with very low birth weight with either post-hemorrhagic (PH) or non-hemorrhagic (NH) hydrocephalus (HDC) were much higher than those in non-HDC controls [217]. No significant difference in sFas levels was observed between patients with PH-HDC and NH-HDC, but CSF sFas levels in patients with PH-HDC with periventricular leukomalacia (PVL) were significantly higher than those in patients without PVL. In contrast, CSF sFasL levels in patients with high-pressure HDC were unchanged from those in healthy controls, irrespective of the cause, namely spina bifida, aqueduct stenosis, and fatal intracerebral hemorrhage [218]. CSF sFas levels in patients with Alzheimer's disease (AD) with mild cognitive impairment (MCI) or pre-MCI were evidently higher than those in non-AD controls [219]. The sFas levels in patients with AD were significantly correlated with the best-performing traditional CSF marker tau protein/amyloid β-peptide 1-42 ratio (T/AB), while the diagnostic performance for mild AD was enhanced by combining the sFas levels with T/AB. CSF sFasL levels in asphyxiated infant patients with severe hypoxic-ischemic encephalopathy (HIE) with grade II and III were significantly elevated compared to those in patients with milder HIE with grade I and healthy controls [220]. The sFasL levels at birth were associated with a predictor of neurological outcomes, Apgar score at 10 min. The combination of sFasL and IL-6 levels predicted the adverse outcomes at 18 months better than the standard biomarker cord-blood pH. CSF sFas levels in patients following severe traumatic brain injury with both Glasgow Coma Scale ≤8 and a positive signal in cranial computed tomography scans were significantly higher than those in healthy controls [221].

3.5.5. Endocrine system diseases [183,222–225]

In the category of endocrine system diseases, a few types of body fluid levels of sFas and sFasL in both type-1 DM (T1DM) and type-2 DM (T2DM) patients have been investigated. SR sFas, but not sFasL, levels in patients with T1DM with normo-albumin urea were significantly lower than those in patients with micro-albumin urea [222]. The SR sFas levels were markedly correlated with cystatin-C-based GFR values even after adjustment for other risk factors, suggesting a strong association between sFas levels and renal function decline in patients with T1DM. In patients with T2DM with diabetic foot lesions (DFL) , both SR sFas and sFasL levels were significantly elevated compared with those in patients without DFL and healthy controls [223]. The sFas levels in the patients still at the stage of lacking DFL were already higher than those in healthy controls. These results indicate the usefulness of sFas and sFasL levels in the early diagnosis and management of T2DM with DFL. SR sFasL levels in patients with T2DM, accompanied by arterial hypertension, were significantly lower than those in healthy controls [224]. Moreover, significantly higher baseline aqueous humor sFasL levels in patients with T2DM with macular edema decreased to the levels of healthy controls after subthreshold micropulse-laser treatment [225]. Higher sFas levels were significantly associated with an increased risk of T2DM development in a prospective population-based cohort study [183].

3.5.6. Dermal system diseases [226–229]

SR sFasL levels in patients with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were significantly higher than those in patients who suffered from ordinary erythema multiforme-type drug eruption and healthy controls [226]. SR sFasL levels in patients with SJS/TEN peaked a few days before the onset of skin detachment and mucosal lesions, and the elevated sFasL levels decreased rapidly within 5 days after onset to the levels in ordinary types of drug-induced skin reaction patients [229], suggesting that sFas levels may be a useful biomarker for early phase diagnosis of SJS/TEN [226,229]. SR sFas and sFasL levels in patients with either drug-or virus-induced skin eruptions and other types of dermal diseases were elevated compared to those in healthy controls, whereas SR sFasL levels in patients with acute viral exanthemas, inflammatory diseases, excluding atopic/autoimmune diseases, and healthy controls were negative [227]. Thus, SR sFasL levels may be a discriminatory biomarker between drug rashes and virus-induced skin eruptions.

3.5.7. Obstetric system diseases [230,231]

No significant differences in both maternal blood-derived SR and umbilical cord blood-derived SR sFasL levels were observed between patients with intrauterine growth restriction (IUGR) and non-IUGR controls [230]. PL DcR3 levels in patients with preeclampsia were significantly lower than those in healthy controls during the same 3rd trimester of pregnancy [231].

3.6. Other miscellaneous diseases [232–244]

The survey results in this section are summarized in Table 6.

3.6.1. Metabolic syndrome-related diseases [232–235]

PL sFasL levels in adult patients with obstructive sleep apnea syndrome (OSAS) and METS were significantly decreased by nasal continuous positive airway pressure treatment, in parallel with ameliorated forearm blood flow responses to reactive hyperemia, which may suggest a correlation between sFasL levels and vascular function in patients with OSAS [232]. PL sFas and sFasL levels in pediatric patients with both severe and mild OSAS were significantly lower than those in non-OSAS controls, and both sFas and sFasL levels in patients with severe OSAS increased after tonsillectomy [234]. PL sFas, but not sFasL, levels in patients with OSAS showed significant negative correlations with two indices reflecting disease activity, the apnea-hypopnea index (AHI) and obstructive AHI. The levels of many circulating cancer-related biomarkers, including PL sFasL, in obese adult patients were significantly decreased after laparoscopic sleeve gastrectomy, which may be related to the previously reported decrease in cancer incidence following bariatric surgery [235]. SR sFasL levels in postmenopausal women with METS were higher than those in non-METS controls; however, the difference lack statistical significance [233].

3.6.2. Aging-related diseases [236–240]

SR sFasL levels in most patients with the progeroid disease Werner syndrome (WS) were markedly higher than those in age-matched young healthy controls, and the sFasL levels were comparable to those in elderly healthy controls [236]. SR sFasL levels in patients with WS were significantly correlated with inflammatory disease-related parameters, including SR CRP and erythrocyte sedimentation rate. PL sFasL levels in patients with age-related macular degeneration (AMD) were significantly elevated compared to those in non-AMD controls [237]. The sFasL levels in female patients with AMD were higher than those in male patients, whereas the opposite tendency was observed in non-AMD controls. Both SR sFas and sFasL levels in women with postmenopausal syndrome (PMS) significantly decrease after treatment with estrogen-based hormone replacement therapy (HRT) [238,240]. The sFasL levels in monozygotic twins with PMS receiving HRT were significantly lower than those in twin patients with PMS without HRT and premenopausal controls. The sFasL levels in patients with PMS either positively or negatively correlated with the SR levels of inflammatory cytokines, including TNF-α and IL-6, depending on HRT usage [240]. PL sFas levels in surviving nonagenarians (NNAG) after a 4-year follow-up period were significantly lower than those in deceased NNAG [239]. The significant correlation between the highest tertile sFas levels in NNAG and mortality remained after adjustment for age, sex, and dwelling status; however, the statistical significance was lost after including other risk factors such as BMI and age-related diseases into the adjustment.

Table 6. Investigations on the possible usage of sFas, sFasL, and DcR3 as clinical biomarkers in other miscellaneous diseases.

Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Metabolic syndrome-related diseases				
sFasL, obstructive sleep apnea syndrome (OSAS) with metabolic syndrome (METS)	Plasma (PL) sFasL levels in patients with OSAS with METS significantly decreased by nasal continuous positive airway pressure (CPAP) therapy for 3 months in parallel with increased forearm blood flow responses to reactive hyperemia (FBF-RH), which reflected an improvement in vascular function.	P: 32 [OSAS with METS (OSAS-MS)] [19 m/13 f; (Mn: 53.9, SD: 8.6)], measurement time-points: before (BF) and after CPAP treatment for 3 months (3M)	PL (sFasL, ng/ml), ELISA (Mn, SD): [OSAS-METS: BF (ca. 3.5, ca. 0.66), 3M-CPAP (ca. 2.9, ca. 0.54)]; $p < 0.01$ (OSAS-METS-CPAP: BF vs 3M), FBF-RH: $p < 0.01$ (OSAS-METS-CPAP: BF vs 3M)	[232]
sFasL, metabolic syndrome (METS) (postmenopausal women)	Serum (SR) sFasL levels in postmenopausal women (PMW) with METS were higher than those in controls without METS. However, the difference was not statistically significant.	P: 100 (total PMW), 57 [with METS (METS)] [all f; (Mn: 56.7, SD: 4.8)], C: 43 (non-METS) [all f; (54.8, 5.4)]	SR (sFasL, pg/ml), MPAA (Mn, SD): [PMW: METS (77.6, 27.6), non-METS (72.8, 28.9)]; $p > 0.05$ (PMW: METS vs non-METS),	[233]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
1. Metabolic syndrome-related diseases				
sFas and sFasL, obstructive sleep apnea syndrome (OSAS) (pediatric)	Plasma (PL) sFas and sFasL levels in pediatric patients suffering from obesity with severe (SEV) and mild (MIL) OSAS were significantly lower than those in non-OSAS controls. However, no statistical difference was observed between SEV-OSAS and MIL-OSAS. In patients with SEV-OSAS, an increasing trend in PL sFasL levels was observed after tonsillectomy treatment (TON). Significant negative correlations of PL sFas, but not sFasL, levels were observed with the apnea-hypopnea index (AHI) and obstructive apnea-hypopnea index (OAHI), reflecting OSAS disease severity.	P: 41 (total OSAS), 20 (SEV)] [11 m/9 f; (Mn: 9.8, SD: 3.5)], 21 (MIL) [12 m/9 f; (8.7, 2.7)], measurement time-points (SEV-OSAS, n = 6): before (BE) and after (AF) TON, C: 17 (non-OSAS) [7 m/10 f; (8.7, 2.8)]	PL (sFas/sFasL, pg/ml), ELISA (Mn, SD): [OSAS: SEV (434.6/49.8, 124.7/18.1), MIL (469.2/55.8, 179.0/18.4)], [non-OSAS (632.3/73.6, 151.1/23.9)], [SEV-OSAS-TON: BE (343.8/45.0, 179.4/15.3), AF (470.6/60.5, 92.7/14.3)]; p = 0.002/p < 0.001 (SEV-OSAS vs non-OSAS), p = 0.015/p = 0.015 (MIL-OSAS vs non-OSAS), p = 0.51/p = 0.29 (OSAS: SEV vs MIL), p = 0.21/p = 0.099 (SEV-OSAS-TON: BE vs AF), Corr. (vs sFas/sFasL): p = 0.027/p = 0.7, r_s = −0.40/r_s = −0.07 (AHI); p = 0.022/p = 0.13, r_s = −0.31/ r_s = −0.20 (OAHI)	[234]
sFasL, obesity (OB) treated by laparoscopic sleeve gastrectomy (LSG)	Plasma (PL) sFasL levels in patients with OB significantly decreased after laparoscopic sleeve gastrectomy (LSG). The reduction in PL sFasL levels in patients with OB may be related to a previously reported decrease in cancer incidence following bariatric surgery.	P: 15 (OB) [8 m/7 f; (Mn: 50.9, SD: 11.9)], measurement time-points: at baseline (BS) and 12 weeks (12W) after LSG	PL (sFasL, arbitrary units), MPAA (Mn, SD): [OB-LSG: BS (224.0, 36.6), 12W (196.6, 39.0)]; p = 0.03 (OB-LSG: BS vs 12W)	[235]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Aging-related diseases				
sFasL, Werner (progeroid) syndrome (WS)	Serum (SR) sFasL levels in most patients with WS were comparable to those in elderly (ELD) healthy controls (HC), but increased in comparison with those in age-matched young (YNG) HC. SR sFasL levels in patients with WS significantly correlated with inflammatory disease-related biomarkers, SR C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).	P: 14 (WS) [6 m/8 f; (Rg: 33–70), C: 21 (HC), 13 (YNG) [4 m/9 f; (15–70)], 8 (ELD) [1 m/7 f; (83–95)]	SR (sFasL, ng/ml), ELISA (Mn, SEM): [WS (3.52, 0.47)], [HC: YNG (1.98, 0.17), ELD (3.94, 0.39)]; $p < 0.05$ (WS vs HC-YNG), $p < 0.01$ (HC: YNG vs ELD), Corr. (vs sFasL in WS): $p < 0.025$, $r = 0.596$ (CRP), $p < 0.024$, $r = 0.598$ (ESR)	[236]
sFasL, age-related macular degeneration (AMD)	Plasma (PL) sFasL levels in patients with AMD were significantly higher than those in non-AMD controls. PL sFasL levels in female patients with AMD were significantly higher than those in male patients, while female non-AMD controls had lower PL sFasL levels than those in male non-AMD controls, regardless of age. PL sFasL levels may be a promising biomarker for the risk assessment of AMD onset.	P: 69 (AMD) [28 m/41 f; (Md: 78, Iqr: 73–82)], C: 161 (non-AMD) [75 m/86 f; (66, 57–74)]	PL (sFasL, ng/ml), ELISA (Md, Iqr): [AMD (0.69, 0.41–0.86)], [non-AMD (0.18, 0.04–0.50)]; $p < 0.0001$ (AMD vs non-AMD), $p < 0.01$ (AMD: male vs female), linear regression analysis [vs cubic root of sFasL in AMD ($n = 58$) and non-AMD ($n = 102$), age (Rg): 61–84]: $p = 0.0009$, $\beta = 2.08$ (AMD status, adjusted for age and gender)	[237]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Aging-related diseases				
sFas and sFasL, postmenopausal estrogen-withdrawal syndrome (PEWS)	Serum (SR) sFas and sFasL levels in patients with PEWS significantly decreased after hormone-replacement therapy with either drospirenone (DSP) or norethisterone acetate (NETA) combined with 17β-E_2 estradiol (EST) for 6 months, compared to baseline levels.	P: 87 (PEWS), 45 [EST plus DSP treatment (EST-DSP)] [all f; (nd)], 42 [EST plus NETA treatment (EST-NETA)] [all f; (nd)], measurement time-points: at baseline (BS), after 6 months (6M) treatment	SR (sFas/sFasL, pg/ml), ELISA (Mn, SD): [PEWS-EST-DSP: BS (6997.4/62.82, 681.8/19.22), 6M (5842.1/54.3, 1386.0/12.99)], [PEWS-EST-NETA: BS (7634.3/62.25, 2446.6/36.12), 6M (6454.1/52.79, 1981.7/28.37)]; p = 0.021/p = 0.038 (PEWS-EST-DSP: BS vs 6M), p = 0.040/p = 0.010 (PEWS-EST-NETA: BS vs 6M)	[238]
sFas, mortality in nonagenarians (NNAG)	Plasma (PL) sFas levels in survived NNAG after a 4-year follow-up period (SUV) were significantly lower than those in deceased NNAG during the period (DEC). The highest tertile of PL sFas levels in NNAG seemed to be associated with higher mortality, but statistical significance was not achieved after adjustment for other risk factors (RFs), including gender, age, dwelling status (DS), high-sensitivity C-reactive protein level, body-mass index, and various age-related diseases.	P: 263 (total NNAG), 115 (SUV) [19 m/96 f; (nd)], 148 (DEC) [46 m/102 f; (nd)], sFasL level: lowest tertile (<6.94 ng/ml) (LsFas), middle tertile (6.94–8.77 ng/ml) (MsFas), highest tertile (>8.77 ng/ml) (HsFas)	PL (sFas, ng/ml), MPAA (Md, Iqr): [NNAG: SUV (7.40, 6.38-8.71), DEC (7.94, 6.74–10.13)]; p = 0.01 (NNAG: SUV vs DEC), % mortality during 4 years (sFas tertile): 51.1 (LsFas), 49.4 (MsFas), 68.2 (HsFas), risk analysis for mortality (HsFas): p = 0.02, HR = 1.58 (95% CI: 1.08–2.33) (unadjusted), p = 0.01, HR = 1.70 (95% CI: 1.15–2.53) (adjusted for age, gender, DS), p = 0.06, HR = 1.59 (95% CI: 0.98–2.61) (adjusted for all other RFs)	[239]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
2. Aging-related diseases				
sFasL, postmenopausal syndrome (PMS) [monozygotic twins (MZ) with/without estrogen-based hormone replacement therapy (HRT)]	Serum (SR) sFasL levels in MZ with PMS (MZ-PMS) using HRT were significantly lower than those in MZ-PMS non-HRT user and premenopausal (PRM) controls. No significant difference was observed between MZ-PMS non-HRT users and PRM. SR sFasL levels in MZ-PMS significantly correlated with levels of inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, and the inhibitory protein for IL-6-mediated signaling sgbp130, partly depending on HRT usage.	P: 22 (total MZ-PMS), 11 [HRT user (HRT)] [all f; (Mn: 57.2, SD: 1.8)], 11 (non-HRT) [all f; (57.2, 1.8)], C: 8 (PRM) [all f; (32.0, 1.6)]	SR (sFasL, pg/ml), ELISA (Mn, SD): [MZ-PMS: HRT (71.68, 32.43), non-HRT (85.61, 33.72)], [PRM (107.09, 12.76)]; $p = 0.021$ (MZ-PMS: HRT vs non-HRT), $p = 0.033$ (MZ-PMS-HRT vs PRM), $p = 0.160$ (MZ-PMS-non-HRT vs PRM), Corr. (vs sFasL, MZ-PMS: HRT/non-HRT): $p = 0.002/p = 0.005$, $r_s = 0.815/r_s = -0.773$ (TNF-α), $p = 0.670/p = 0.026$, $r_s = -0.145/r_s = -0.665$ (IL-6), $p = 0.022/p = 0.789$, $r_s = 0.709/r_s = 0.098$ (sgbp130)	[240]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Transplantation-related diseases				
sFasL, acute graft-versus-host disease (AGVHD) after allogeneic hematopoietic stem cell transplantation (AHSCT)	Plasma (PL) sFasL levels in patients with AHSCT-received at AGVHD onset point (AGVHD) were significantly higher than those in patients who developed AGVHD later (pre-AGVHD), recipients who did not develop AGVHD (non-AGVHD), and healthy controls (HC) at baseline. However, PL sFasL levels in pre-AGVHD patients increased progressively up to day 21 and showed a significant elevation compared to non-AGVHD controls. PL sFasL levels in the early phase after AHSCT may be a useful biomarker for early diagnosis and prediction of AGVHD onset.	P: 49 (total AGVHD and pre-AGVHD) [26 m/24 f; (Md: 31, Rg 18–42)], C: 31 (non-AGVHD) [14 m/16 f; (29, 15–41)], 35 (HC) [18 m/17 f; (31, 15–40)], measurement time-points: at baseline (BS), 7 days (7D), 14 days (14D), 21 day (21D), 28 day (28D) after AHSCT	PL (sFasL, ng/ml), ELISA (Mn, SD): [AGVHD (0.34, 0.02)], [pre-AGVHD: BS (0.21, 0.03), 7D (0.19, 0.04),14D (0.17, 0.03), 21D (0.25, 0.01), 28D (0.19, 0.01)], [non-AGVHD: BS (0.17, 0.02), 7D (0.16, 0.03), 14D (0.14, 0.02), 21D (0.17, 0.01), 28D (0.18, 0.02)], [HC (0.24, 0.01)]; $p < 0.001$ (AGVHD vs non-AGVHD-BS), $p < 0.05$ (AGVHD vs pre-AGVHD-BS, HC; 21D: pre-AGVHD vs non-AGVHD), p = ns (BS, 7D, 14 D, 28D: pre-AGVHD vs non-AGVHD)	[241]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
3. Transplantation-related diseases				
sFasL, allograft rejection (AR) after kidney transplantation (KT) (pediatric)	Serum (SR) sFasL levels in pediatric KT recipients (PKTR) were significantly higher than healthy controls (HC). No statistically significant difference in SR sFasL levels was observed between PKTR with allograft rejection (AR) and those without AR. However, SR sFasL levels correlated with ischemia time (IT) in the transplantation, and the level was identified as an independent risk factor significantly affecting AR in PKTR.	P: 47 (total PKTR) [29 m/18 f; (Mn: 9.63, SD: 3.33)], 17 [with AR (AR)] [10 m/7 f; (9.37, 3.56)], 30 (non-AR) [19 m/11f; (10.09, 2.95)], C: 20 (HC) [12 m/8 f; (8.7, 4.51)], donor: [nd/nd (36.49, 7.44)]	SR (sFasL, pg/ml), ELISA (Mn: SD): [total PKTR (548.25, 298.64)], [HC (143.17, 44.55)], [PKTR: AR (567.70, 279.87), non-AR (507.85, 342.80)]; $p = 0.0001$ (total PKTR vs HC), $p = 0.56$ (PKTR: AR vs non-AR)], Corr. (vs sFasL): $p = 0.005$, $r = 0.448$ (IT), multiple regression analysis for risk factors affecting AR: $p = 0.018$, $\beta = 0.464$ (sFasL)	[242]

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Target markers, target diseases (abbreviations/ disease types)	Primary findings regarding possible clinical uses for diagnosis, treatment, or prediction, related to the target markers and diseases	Cohort characteristics: patients (P)/controls (C): total/subcategory sample numbers (types), [male (m)/female (f) numbers; (ages in years): mean (Mn), SD/SEM, median (Md), whole range (Rg)/interquartile range (Iqr)], measurement time-points	Sample types (target markers, unit), evaluation methods (statistical indices); observed values [mean (Mn), SD/SEM, median (Md), whole range (Rg)/ interquartile range (Iqr)]; representative indices in various statistical analyses	Refs.
4. Envenomation and smoking				
sFas and sFasL, scorpion envenomation (SE) (pediatric)	Serum (SR) sFas and sFasL levels in pediatric victims who suffered from severe scorpion envenomation (SE) were significantly higher than those in the victims who suffered from mild SE and healthy controls (HC). The non-survivors (non-SUV) had significantly higher levels than those in the survivors (SUV). SR sFas levels strongly correlated with the logistic organ dysfunction system (LODS) score. SR sFas levels could predict the outcome of pediatric SE.	P: 46 (total SE) [33 m/13 f; (Rg: 2–13)], 25 (total SEV-SE) [nd/nd; (Mn: 4.98, SEM: 0.77)], 18 (SUV), 7 (non-SUV), 21 [mild SE (MIL-SE)] [nd/nd; (5.02, 0.85)], C: 20 (HC) (gender- and age-matched)	SR (sFas/sFasL, ng/ml), ELISA (Mn, SEM): [total SE (5.54/0.60, 0.35/0.03)], [total SEV-SE (6.18/0.66, 0.58/0.05)], [SEV-SE: SUV (4.88/0.59, 0.26/0.03), non-SUV (9.53/0.85, 1.28/0.13)], [MIL-SE (4.79/0.53, 0.27/0.04)], [HC (3.89/undetectable, 0.33/nd)]; $p < 0.001$/$p < 0.05$ (SEV-SE: SUV vs non-SUV), $p < 0.05$/$p < 0.05$ (SE: SEV vs MIL), sFas: $p < 0.01$(total SE, SEV-SE vs HC), $p < 0.05$ (MIL-SE vs HC), Corr. (vs sFas): $p < 0.0001$, $r = 0.81$ (LODS score)	[243]
sFas, cigarette smoking (CS)	Serum (SR) sFas levels in current cigarette smokers (CCS) and past cigarette smokers (PCS) were significantly higher than those in never smokers (NCS), with higher values in CCS than those in PCS. No statistically significant correlation was observed between SR sFas levels among CCS and the number of smoked cigarettes per day, however, the least square mean (LSM) of SR sFas levels peaked at 20 cigarettes per day.	P: 3426 (total CS), 2175 (CCS) [all m; (Mn: 61.7, SD: 7.6)], 1251 (PCS) [all m; (64.0, 7.2)], C: 998 (NCS) [all m; (62.7, 8.4)]	SR (sFas, ng/ml), ELISA (Mn, 95% CI): [CCS (2.36, 2.30–2.43)], [PCS (2.29, 2.22–2.36)], [NCS (2.21, 2.14–2.27)]; $p < 0.0001$ (CCS vs NCS), $p = 0.0009$ (PCS vs NCS), LSM of sFas (number of CS per day): 2.28 (1–5), 2.37 (6–10), 2.40 (11–15), 2.42 (16–20), 2.34 (21–25), 2.35 (26–30), 2.41 (>30) (adjusted for area, age category, body-mass-index, drinking and marital statuses, education, green-leaf vegetables consumption)	[244]

3.6.3. Transplantation-related diseases [241,242]

PL sFasL levels in patients who underwent allogeneic hematopoietic stem cell transplantation (AHSCT) were largely affected by the status of acute graft-versus-host disease (AGVHD) [241]. The sFasL levels in AHSCT patients at the AGVHD onset were significantly higher than those in patients who developed AGVHD later (pre-AGVHD) and non-AGVHD developed controls at baseline. sFasL levels in patients with pre-AGVHD, but not in non-AGVHD controls, increased progressively in the early phase after AHSCT, suggesting that sFasL levels may be a useful biomarker for early diagnosis and prediction of AGVHD onset. SR sFasL levels in pediatric kidney transplant recipients (PKTR) were significantly higher than those in healthy controls [242]. A statistically significant difference in sFasL levels was not observed between PKTR with acute rejection (AR) and those without AR; however, a multiple linear regression analysis demonstrated that sFasL levels were a significant independent risk factor affecting AR onset.

3.6.4. Envenomation and smoking [243,244]

SR sFas and sFasL levels in pediatric patients on admission to the hospital were reflected in the severity from scorpion envenomation (SE). Patients with severe SE had higher SR sFas and sFasL levels than those with mild SE and healthy controls; in particular, the levels in non-surviving patients were remarkably higher than those in survivors [243]. The sFas levels strongly correlated with the logistic organ dysfunction system score, and therefore, could predict the outcome of pediatric SE. SR sFas levels in current and past cigarette smokers were significantly elevated compared to those in never smokers [244]. Despite no statistically significant correlation between sFas levels among current smokers and the number of cigarettes smoked, the least mean square of the sFas levels in current smokers peaked at 20 cigarettes per day.

4. Conclusions and perspectives

The present survey revealed that many body fluid levels of sFas, sFasL, and DcR3 in patients suffering from a wide variety of diseases could potentially be used for the assessment of various clinical states. The potential targets ranged over diseases not only directly related to Fas ligand-induced apoptotic cell death in their onset mechanisms, but also many more general inflammation-related diseases. This may be reasonably well explained by the existence of substantial connections between Fas receptor-mediated cell death and inflammation. However, further studies in various relevant fields will be essential before they are established as effective disease biomarkers that can contribute to practical strategies for therapeutic interventions. The variation direction and degree of upregulation and downregulation of the marker levels largely depended on the diseases, characteristics of the targeted patient cohorts, and time points for collecting the specimens, even within a range of the same or similar disease categories. SR sFasL levels in patients who suffered from cancer, including breast, hepatocellular, small-cell lung, and bladder cancers, were significantly higher than those in healthy controls in most cases, while the sFasL levels in patients with head-and-neck and prostate cancers were significantly lower than those in healthy controls. SR Fas levels in patients suffering from autoimmune diseases such as SLE, RA, GD, and SS were significantly higher than those in the healthy controls; in contrast, the sFas levels in patients with another autoimmune disease

such as familial Mediterranean fever with amyloidosis were significantly lower than those in healthy controls. The correlation between the disease activity index and SR DcR3 levels in adult and pediatric asthma patients behaved conversely, regarding the coexistence of atopy symptoms. A remarkable time-point dependence in SR/PL sFasL levels was observed in patients with SJS/TEN or in recipients of AHSCT affected by AGVHD. As frequently described in the respective disease-category sections, although the reviewed soluble markers could commonly inhibit the apoptotic cell death mediated by Fas receptor, the variation behaviors in each of the sFas, sFasL, or DcR3 levels were not always identical even in the cases of the same diseases. In addition to choosing the suitable patient ranges and most appropriate marker(s) among sFas, sFasL, and DcR3, further extensive investigations into the best timing and situation as well as enrollments of a larger patient cohort to increase the statistical accuracy for arranging and settling the remaining issues, would be required to maximize the usefulness of the markers for the individual targeted diseases.

Clinical assessments using non-invasive body fluid biomarkers, including sFas, sFasL, and DcR3, may become one of the most attractive treatment strategies that are indispensable for personal precision medicine if cost-effective and by employing a small sample size. At present, the methods for quantitative detection of sFas, sFasL, and DcR3 levels in body fluids using traditional enzyme-linked immunosorbent assays, as well as more recently developed multiplex immunoassays, rely on immunoglobulin-type primary antibodies, which are produced using individual or cultured cells from higher animals. In the future, recently developed functionalized derivatives of recombinant sFas and sFasL molecules produced by less expensive biotechnological techniques using other protein-expression hosts such as *Pichia pastoris* [245,246] and *Bombyx mori* [247], and their application to DcR3 may substitute primary antibodies, because they are applicable to direct detection of native-style interactions either between sFasL and sFas or between sFasL and DcR3 in the nM range of binding constants [248]. They can avoid heterogenous sensitivity against the same target marker among immunoglobulin-type products, which may be derived from the difference in recognizing epitope sites. Moreover, further development of more advanced reagents and sophisticated systems for detection under difficult circumstances with high sensitivity is essential for facilitating the translation of the biomarkers surveyed in this research into practical medical applications. The proposed process is summarized in Figure 1 for the translation of sFas, sFasL, and DcR3 levels in body fluids into practical clinical biomarkers in individual Fas-mediated apoptosis/inflammation-related diseases.

The selection of therapeutic strategies for diseases using combinations of clinical biomarkers alone is not always a straightforward process. However, new developments in effective body fluid biomarkers can substantially contribute to the effective treatment of various diseases, directly leading to novel, non-invasive methodologies for efficient diagnosis of disease status at relatively low costs. Successful translation of sFas, sFasL, and DcR3 may provide important contributions to the treatment of many diseases across medical disciplines, including unexplored diseases.

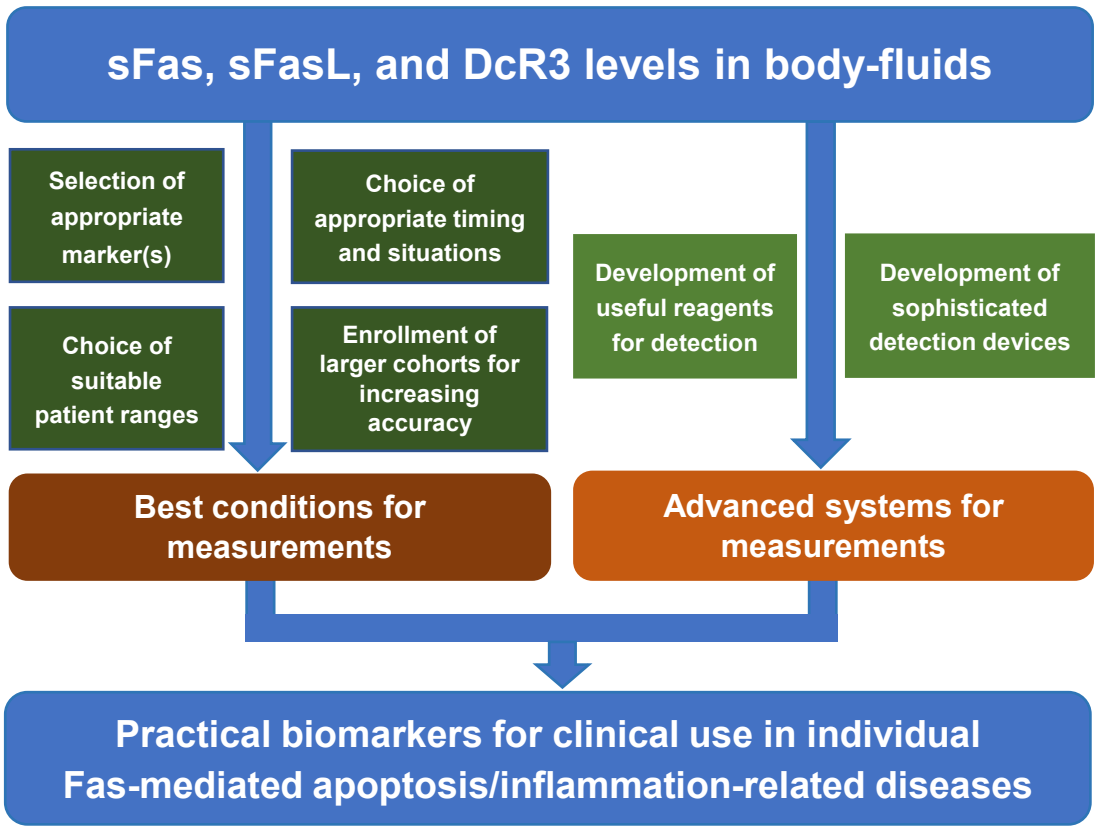

Figure 1. Scheme for the translation of sFas, sFasL, and DcR3 levels into practical biomarkers in clinical medicine.

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Conflict of interests

The author declares that there is no conflict of interest.

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