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The clinicopathological implications of serum IL-33 and sST2 as cancer biomarkers: A narrative review

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ABSTRACT

Background: Interleukin (IL)-33 and its receptor, soluble suppression of tumorigenicity 2 (sST2), are key players in the immune response and cancer biology. IL-33 can promote tumorigenesis by enhancing cancer cell proliferation and modulating the immune environment to support tumor growth. Conversely, it can also bolster anti-tumor immunity by recruiting and activating immune effector cells. IL-33 plays a role in multiple aspects of cancer biology, such as promoting immune evasion, tumor growth, and metastasis.
Objective: This study intends to assess the prognostic significance of serum IL-33 and sST2 in cancer and their association with clinicopathologic characteristics (CPC).
Material & methods: Scopus, PubMed electronic databases and other sources were searched and analysed from 2008–2025. The quality of the study was assessed using the Newcastle-Ottawa Quality Assessment Scale.
Results: A total of forty-four studies meeting the inclusion criteria were analyzed. These studies primarily employed an observational and analytical designs, with the majority conducted in the Southeast Asian region, particularly in China. Among the studies investigating serum IL-33 levels in cancer, 68% (26/38) reported elevated serum IL-33 levels, with the majority focusing on hepatocellular carcinoma (HCC) and non-small cell lung cancer (NSCLC), followed by breast (BC) and colon rectal cancer (CRC). Additionally, 85% (22/26) of the reports found a significant association between serum IL-33 expression in cancer and CPC. For regulating the availability and activity of IL-33, sST2, a decoy receptor that binds to IL-33, is crucial. Of the studies assessing sST2 in cancer, 55% (12/22) showed elevated sST2 levels, with most focusing on HCC, followed by BC and CRC. Furthermore, 54% (7/13) of these studies identified a significant correlation between sST2 levels and CPC.
Conclusion: The detection of increased serum IL-33 across various malignancies highlights its potential as an emerging biomarker for cancer detection and prognosis. Similarly, elevated sST2 levels have been observed in different cancers and are linked to poor prognosis, further highlighting its potential as a biomarker for tumor progression. The IL-33/ST2 signaling pathway could offer new cancer treatment strategies by enhancing immune responses while mitigating tumor-promoting effects. This study explores the roles of IL-33 and sST2 as biomarkers, their relevance in cancer diagnostics and therapeutics, and their correlation with clinical outcomes across different cancer types.

1. Introduction

Cancer development is often associated with immune evasion and inflammation that promotes tumor growth, with interleukins (ILs) playing a central role in these immune-inflammatory processes. ILs are involved in complex tumor regulatory networks, influencing tumor progression through mechanisms such as inflammation, malignant transformation, growth, proliferation, angiogenesis, invasion, migration, and modulation of anti-tumor immunity. Recent clinical studies have revealed abnormal serum cytokine levels in cancer patients, which are strongly correlated with tumor invasion, metastasis, treatment response, postoperative recurrence, and prognosis.[1] However, the exact role of serum ILs in cancer remains unclear. In particular, Interleukin-33 (IL-33) has recently been implicated in both tumorigenesis and tumor immunity, with emerging research suggesting its significant involvement in cancer development.[2,3]

Interleukin (IL)-33, a cytokine discovered in 2005 as part of the IL-1 family, exerts its effects through the Suppression of Tumorigenicity 2

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(ST2) receptor, which exists in both a soluble form (sST2) and a transmembrane variant (ST2L).[4–6] IL-33 is a nuclear cytokine expressed by various cells, including endothelial cells, fibroblasts, epithelial cells, and immune cells such as dendritic cells and macrophages.[4,5] It is released during mechanical or oxidative stress, necrosis, or cell activation, functioning as an alarmin. Upon tissue injury or necrosis, IL-33 signals through the ST2 receptor complex, comprising IL-1RL1/ST2 and IL-1RAP, which activates downstream signaling. This triggers NF-κB, p38, JNK, and ERK pathways, leading to the expression and secretion of cell-specific cytokines and chemokines. These pathways promote effects such as cell proliferation, survival, amphiregulin expression, epithelial-mesenchymal transition (EMT), and inhibition of adaptive immunity.[7–10] In contrast, sST2 acts as a decoy receptor, reducing IL-33's biological activity and availability.[6]

IL-33 plays multiple roles in immune regulation by activating Type I T helper (Th1) cells, Type II T helper (Th2) cells, Natural Killer (NK) cells, and $CD8^+$ T cells, but it is mainly linked to the activation of Type 2 immune responses.[8] IL-33 was initially depicted as a strong initiator of type 2 immune responses, activating various cell types, including Th2 cells, type 2 innate lymphoid cells (ILC2s), mast cells, basophils, eosinophils, and myeloid-derived antigen-presenting cells like macrophages and dendritic cells (DCs). IL-33-exposed DCs and mast cells promote the expansion of regulatory T cells (Tregs) and induce the production of suppressive cytokines like IL-10 and TGFβ.[11,12] Malignant tumors often impair host immune responses, and Th2 type cytokines (IL-4, IL-5, IL-10, IL-13) have been shown to down-regulate tumor specific immune response by inhibiting tumor antigen presentation.[2]

Tumorigenesis is typically linked to the suppression of Th1-mediated immunity and the enhancement of Th2 responses. The IL-33/ST2 interaction drives naïve T cells toward a Th2 phenotype, and blocking this pathway can boost anti-tumor Th1 responses.[13] IL-33 influences the tumor microenvironment (TME) by remodeling tissues, inducing angiogenesis, and promoting tumor progression through M2 macrophage polarization and the activation of immunosuppressive cells, such as myeloid - derived stem cells (MDSCs) and Tregs.[11] IL-33 is now recognized not only as an inducer but also as a prognostic marker of cancer, contributing to tumorigenesis, proliferation, survival, and metastasis. However, recent studies show IL-33 also supports Th1 responses, stimulating Th1 immune cells, NK cells, iNKT cells, and $CD8^+$ T lymphocytes. The anti-tumor effects of IL-33 depend on Th1 responses within infiltrated immune cells and can activate type 1 immune responses through TNF-α and IFN-γ production by $CD8^+$ T cells, NK cells, or iNKT cells.[13] Thus, IL-33 may play a dual role, supporting both pro- and anti-tumor responses, depending on tumor context, expression levels, bioactivity, and the inflammatory environment[14] (Fig. 1).

IL-33 is released in the TME and can influence tumor-associated inflammation, making it a candidate for assessing tumor dynamics.[8] It is recognized as a key mediator in inflammation-related carcinogenesis.[6] Exogenous IL-33 appears to function primarily as an immunoregulatory cytokine, modulating Th2 immunity rather than acting as a pro-inflammatory cytokine.[2] Recent research indicates that IL-33 might contribute to tumorigenesis.[2,4] It has been linked to tumor biology, contributing to tumor development and metastasis.[7] IL-33 can be detected not only in the tumor environment, but also in the serum of cancer patients.[8] Raised serum IL-33 levels have been documented in multiple studies involving cancer patients. Increased expressions of IL-33 are detected in the serum and tumor tissues of gastric, lung, hepatocellular, and colorectal cancers, showing correlations with various prognostic factors.[2,3,15–19] On the other hand, some studies emphasize IL-33 as a potent stimulator of anticancer immunity, enhancing the stimulation of cytotoxic $CD8^+$ T cells.[20–25] In contrast, data on sST2 in cancer patients are limited and inconsistent. sST2 is a soluble receptor for IL-33 that can also modulate immune response, functioning as a trap for IL-33.[6] Elevated sST2 have been associated with various cancers.[6,26] Higher serum levels of sST2 have been associated with worse prognosis in several malignancies, indicating its potential role in risk stratification.[6,16,26–30]

This review summarizes the key references regarding IL-33 and sST2 within serum as diagnostic tools and risk predictors for cancer.[2] This study aims to assess the prognostic value of serum IL-33 and sST2 in cancer and explore their correlation with clinicopathologic characteristics. This article examines studies on IL-33 and sST2 across various

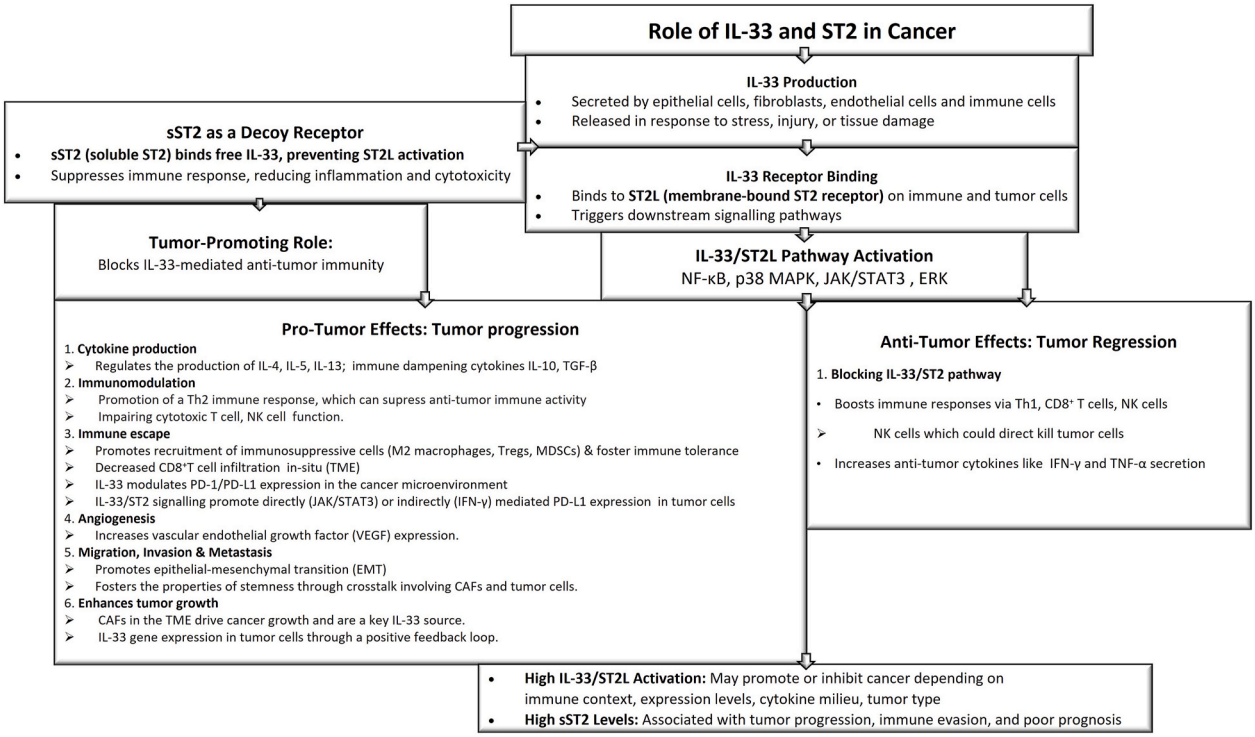

Fig. 1. Flowchart: Role of IL-33 and ST2 in cancer.

cancers, exploring their potential as biomarkers and emphasizing the clinical relevance.

2. Material and methods

2.1. Search strategy

Both online searches and manual browsing were utilized to gather relevant literature. A comprehensive search was conducted using the World Wide Web as the primary tool, with studies sourced from two leading electronic databases: Scopus and PubMed. The search spanned from 2008 to 2025, focusing on research that investigated the varying expression of IL-33 and sST2 in the serum of cancer patients. In addition, further relevant literature within the inclusion criteria was identified through manual searching.

Two researchers independently conducted searches of the electronic databases using MeSH terms and keywords, including "IL-33," "Serum IL-33," "Interleukin-33," "ST2," "soluble ST2," "Suppression of Tumorigenicity 2," and "Cancer." Since the majority of relevant articles were obtained from the Scopus database, the following keywords were employed. (TITLE-ABS-KEY ("IL-33″) OR TITLE-ABS-KEY (“Serum IL-33”) OR TITLE-ABS-KEY (“Interleukin-33”) AND TITLE-ABS-KEY (“ST2”) OR TITLE-ABS-KEY (“Soluble ST2”) OR TITLE-ABS-KEY (“Suppression of tumorigenicity 2”) AND TITLE-ABS -KEY (“Cancer”)) AND PUBYEAR >2008 AND PUBYEAR <2026 AND (LIMIT-TO (LANGUAGE, “English”)).

2.2. Eligibility criteria

The selected studies focused on the varying expression of IL-33 and sST2 in the serum of cancer patients, specifically analytical and observational research that explored their role and clinical significance. Only relevant original articles and systematic reviews published in English were included in this review. Studies that examined IL-33 and sST2 levels in the serum or plasma of cancer patients using ELISA were considered.

Exclusions encompassed research on IL-33 and ST2 expression in tumor tissues from cancers such as lung, breast, endometrial, ovarian, gastric, hepatic, prostate, and colon. Studies assessing IL-33/ST2 in other body fluids, tumor tissues of cancer patients, implementing methods like immunohistochemistry (IHC), Western blot (WB), flow cytometry (FC), and quantitative real time polymerase chain reaction (qRT-PCR) were also excluded. Additionally, research involving cancer cell lines, animal models. Investigations of IL-33/sST2 in inflammatory, allergic, immunological, and infectious diseases was not included. Other exclusions were studies on IL-33 and sST2 in cancer patients with different objectives, such as soluble ST2 as a cardiac biomarker (for cardiac dysfunction) in patients undergoing chemotherapy. General reviews, randomized controlled trials (RCTs), editorials, short surveys, and conference papers were excluded.

2.3. Data extraction

Two researchers independently assessed the literature from electronic databases. The process started with removing duplicates, followed by screening titles, abstracts, and keywords to exclude irrelevant studies. Full-text articles were then reviewed for inclusion. Eligibility was determined by two reviewers (X, Y), with articles included only if both agreed. In case of disagreement, a third reviewer (Z) was consulted.

Data for this review were manually extracted from the selected studies. Title, abstract, and full-text screening were independently conducted by authors (X and Y), with discrepancies resolved by a third author (Z). X extracted the necessary details, while Y and Z cross-verified for accuracy. The data were recorded in an excel sheet. The following parameters were extracted: publication details (Authors, Year, Journal), demographics (Ethnicity), experiment details (Expression of serum IL-33 and sST2 levels in the cancer group and other comparison groups, such as pre-cancer, chronic pathologies like cirrhosis, and healthy controls (HC)), the relationship between clinicopathologic characteristics (CPC) and IL-33/sST2 expression, and clinical outcomes (survival correlation with IL-33/sST2 expression).

2.4. Studies quality assessment

The methodological quality of the selected research articles was assessed using Newcastle-Ottawa Scale (NOS). The results from NOS were converted into the Agency for Healthcare Research and Quality (AHRQ) standards of ‘good, ‘fair’ and ‘poor’ quality.

3. Results

3.1. Study selection

This review includes a total of 44 studies published in English, selected based on predefined eligibility criteria. Initially, 399 records were identified through electronic databases (n = 399), and 28 additional records were found via manual searches (n = 28). After removing 138 duplicates, 289 articles were screened based on their titles and abstracts, resulting in the exclusion of 234. The remaining 55 articles were deemed eligible for full-text retrieval, of which 53 were accessible for further evaluation. Following a detailed assessment, 9 reports were excluded, leaving 44 studies for final inclusion. The reasons for exclusion are outlined in the flowchart (Fig. 2) and Supplementary Table 1. Detailed descriptions of each study are provided in Tables 1 and 2. The extracted data include information on the type of cancer, serum IL-33 and sST2 expression levels, their associations with clinicopathological characteristics and outcomes, as well as their clinical implications.

3.2. Study quality assessment

The highest rating of nine stars was not achieved by any study, as each was found to have some risk of bias or unclear methodological reporting. The NOS ratings were converted to AHRQ standards, with twenty-five studies rated as good[2–4,6,19–23,26–28,30,31,34,36–42,44,46,47] and nineteen as fair.[15–18,24,25,29,32,33,35,43,45,48–54]

3.3. Study characteristics

Forty-four studies meeting the inclusion criteria were analyzed,[2–4,6,15–54]. These studies primarily employed observational and analytical designs, with the majority being cross-sectional and case-control studies. Most were conducted in Southeast Asia, particularly in China. Tables 1 and 2 provide detailed characteristics of each study included in this review. The objectives of the included studies align with the overall purpose of the review.

Serum IL-33 was assessed in thirty-eight studies (Table 1), while sST2 was evaluated in twenty-two studies (Table 2). Sixteen studies examined both serum IL-33 and sST2 in cancer, six studies focused solely on sST2, and twenty-two studies focused exclusively on serum IL-33 in cancer. The association between serum IL-33 and cancer progression was evaluated in 26 reports, while twelve reports examined the relationship between serum IL-33 and survival. Thirteen reports assessed the link between sST2 and CPC, and six reports investigated the relationship between serum sST2 and survival.

3.4. Study outcome

Among the studies investigating serum IL-33 levels in cancer, 68 % (26/38) reported elevated serum IL-33 levels, with the majority focusing on hepatocellular carcinoma (HCC) and non-small cell lung cancer (NSCLC), followed by breast (BC) and colon rectal cancer (CRC). The detection of increased serum IL-33 across various malignancies

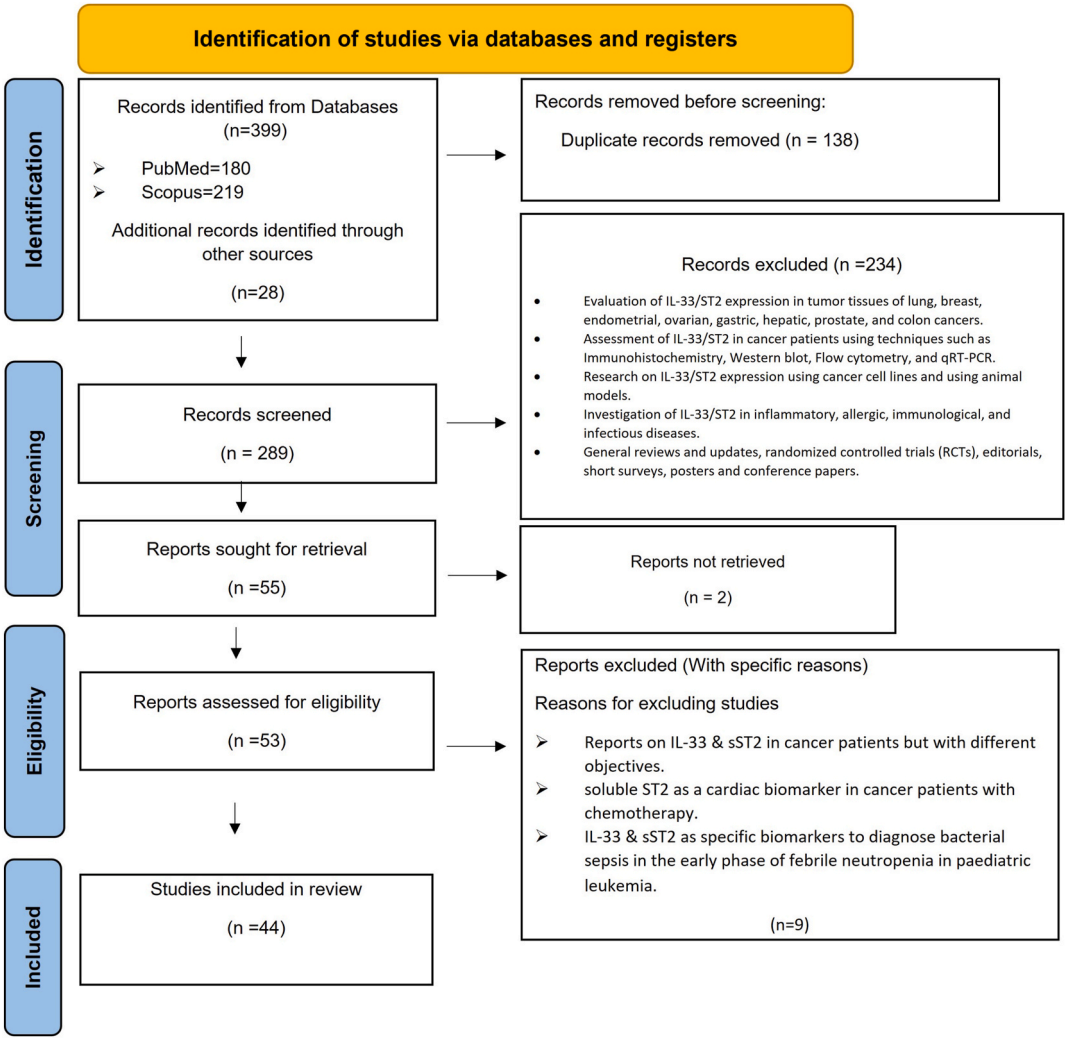

Fig. 2. Flowchart: Overview of the systematic review process following the PRISMA guidelines.

highlights its potential as a biomarker for cancer detection and prognosis. Additionally, 85 % (22/26) of the reports found a significant association between serum IL-33 expression in cancer and CPC. 58 % of studies (7/12) showed significant relation between serum IL-33 and survival outcomes.

sST2, a decoy receptor that binds to IL-33, plays a crucial role in regulating the availability and activity of IL-33. Among the studies assessing sST2 in cancer, 55 % (12/22) reported elevated sST2 levels, with most focusing on HCC, followed by BC and CRC. Elevated sST2 levels have been observed across various cancers and are associated with poor prognosis, further emphasizing its potential as a biomarker for tumor progression. Additionally, 54 % (7/13) of these studies found a significant correlation between sST2 levels and CPC, while 50 % (3/6) reported a significant association between serum sST2 levels and survival outcomes.

Sixteen reports evaluated serum IL-33 and sST2 simultaneously in cancer patients, 44 % (6/16) studies noted significant elevation in serum IL-33 and sST2 levels in cancer patients than the control group (Tables 1 and 2).

Receiver operating curve (ROC) curve analysis was conducted to evaluate the diagnostic performance of serum interleukin-33 (IL-33) as a biomarker in cancer patients, focusing on determining the optimal cut-off value, sensitivity, and specificity. Data from nine studies, which reported varying IL-33 levels, were analyzed to calculate the area under the curve (AUC), reflecting IL-33's ability to distinguish between cancer and non-cancer conditions.[2,3,15,21,26,31,33,48,49] The optimal cut-off value was identified to balance sensitivity and specificity. This analysis highlights IL-33's potential as a diagnostic marker and emphasizes the need for standardization and validation across different cancer types.

4. Discussion

4.1. Serum IL-33 and sST2 in cancer

Recent research has focused on IL-33 and sST2 across various tumor types.[26] IL-33 and sST2 serum levels have demonstrated potential as promising biomarkers for diagnosing different cancers. Elevated levels may correlate with tumor burden and disease stage. Studies have shown that patients with higher quantities of IL-33 or sST2 often experience worse outcomes, such as an increased likelihood of metastasis or reduced survival rates.[6,16,27–29]

4.2. Serum IL-33 and sST2 in gastric cancer (GC)

Current reports have highlighted the predictive value of IL-33 levels in serum of GC. Sun et al.[2] employed enzyme-linked immunosorbent assay (ELISA) to assess IL-33 in GC patients, revealing significantly higher levels compared to HC. This increase correlated with adverse parameters like advanced disease stages, distant metastasis, and depth of invasion, suggesting IL-33 could serve as a valuable prognostic

Table 1
Studies investigating serum IL-33 in cancers and associated clinical implications.

SL. No	Authors	Year	Type of CA	IL-33 ↑	IL-33 ↓	NC	Other Biomarkers investigated	Association/ correlation with CPC	Survival outcomes	Clinical implications
								Parameters		
1	**Sun et al.**[2]	2011	**GC**	+	–	–	CEA^{NS}, $CA\text{-}19\text{-}9^{NS}$	Yes/S; **DI, MS, TS**	Yes/S	Serum IL-33 could serve as a valuable biomarker for forecasting the prognosis of GC.
2	**Bergis et al.**[26]	2016		–	–	+	$sST2^{@}$	Yes/S; **DD**	Yes/NS	The IL-33/sST2 ratio may provide a novel and intriguing method for identifying GC patients.
3	**Hu et al.**[31]	2017		+	–	–	–	Yes/S; **DM**	Yes/S	The degree of decline in serum IL-33 following chemotherapy may serve as an indicator of PFS.
4	**Naumnik et al.**[32]	2011	**NSCLC**	+	–	–	IL-20, IL-29, Galectin $3^{@}$	Yes/S; **MS**	NA	The clinical utility of serum IL-33, IL-20, Galectin-3, and IL-29 in diagnosing cancer appears to be limited.
5	**Naumnik et al.**[33]	2012		–	–	+	IL-27, IL-29, IL-31	Yes/NS	Yes/NS	*
6	**Hu et al.**[3]	2013		+	–	–	–	Yes/S; **TS**	Yes/S	IL-33 shows potential as a diagnostic and prognostic marker for NSCLC, independent of treatment.
7	**Petrovic et al.**[15]	2014		+	–	–	–	Yes/S; **TS**	Yes/S	IL-33 demonstrated strong diagnostic performance for NSCLC.
8	**Kim et al.**[20]	2015		–	+	–	–	Yes/S; **TS**	NA	IL-33 levels are inversely associated with LC progression.
9	**Xu et al**[16]	2018		+	–	–	sST2, IL-4	NA	NA	In the NSCLC microenvironment, the IL-33/ST2 interaction promotes a Th2 response, potentially supporting Tg.
10	**Pang et al.**[27]	2020		+	–	–	sST2, IL-17A, $IFN\gamma^{\#}$, IL-$10^{@}$, IL-$4^{@}$	NA	NA	Elevated levels of IL-33 and ST2 in NSCLC patients may shift the Th1/Th2 cytokine balance in the immune response.
11	**Liu et al.**[34]	2014	**BC**	+	–	–	ER, PR, HER2, Ki-67, IL-33, Il-12, IL-13, IL-17, IFNγ, TNFα	Yes/S; **ER, KI-67, FH**	NA	IL-33 may be vital in BC progression and serve as a useful biomarker for predicting disease advancement, metastasis, the malignant potential and immunosuppression of BC.
12	**Lu et al.**[28]	2014		+	–	–	sST2, $VEGF^{@}$, ER, PR, HER2, Ki-67	Yes/NS	Yes/NS	*
13	**Yang et al.**[29]	2015		+	–	–	sST2, $VEGF^{@}$, MMP-$11^{@}$, PDGF-$C^{@}$	NA	NA	IL-33 and sST2 may act as non-invasive diagnostic markers BC.
14	**Haghbin et al.**[35]	2022		+	–	–	–	NA	NA	IL-33 is a key factor distinguishing IGM and BC patients from HC.
15	**Zhang et al.**[17]	2012	**HCC**	+	–	–	IFNα, IFNγ	Yes/S; **MS**	NA	IL-33 could serve as a valuable biomarker for tracking the growth and metastasis.
16	**Bergis et al.**[6]	2013		–	–	+	sST2, AFP, ALT, AST, INR, Bilirubin, CRP, Na, Creatinine	Yes/S; **TS**	Yes/NS	*
17	**Shen et al.**[21]	2018		–	+	–	IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IFN-γ, sCD40L, TNFα	NA	NA	Researchers identified a distinct signature of eight (IL-1β, IL-6, IL-10, IL-17A, IL-25, IL-4, IL-22, IL-33) peripheral blood cytokines for HCC detection.
18	**Wang et al**[22]	2022		–	+	–	sST2, Perforin, Granzyme B	NA	NA	IL-33 enhances the killing activity of $CD8^{+}$ T cells by promoting perforin and granzyme B secretion, presenting a potential new target for HCC therapy.
19	**Askoura et al.**[37]	2022		+	–	–	IL-$17^{@}$, IL-$25^{@}$, $AST^{@}$, $ALT^{@}$, IL-10, $IFN\gamma^{@}$, γ-GT, Bilirubin $^{@,}$ Zinc $levels^{@}$	NA	NA	IL-33 is significantly involved in the progression of liver inflammation and fibrosis in chronic hepatitis C.
20	**Pan et al**[30]	2023		–	–	+	sST2	NA	NA	IL-33 mRNA and serum levels were similar in HCC patients and HC.
21	**Yasen et al.,**	2024		+	–	–	sST2, $MIF^{@}$	Yes/S; **Ts, TG, LNM, TS**	NA	Elevated IL-33 levels were linked to aggressive clinicopathologic traits, suggesting IL-33/ST2 signaling as a potential diagnostic biomarker and therapeutic target for ICC.
22	**O'Donnell et al.**[23]	2016	**CRC**	–	+	–	sST2	NA	NA	The IL-33/ST2 signalling axis may have a protective effect in colon carcinogenesis.
23	**Xie et al.**[18]	2016		+	–	–	CEA, CA 19-9	Yes/S; **TG, TL**	NA	IL-33 may be linked to tumor progression in CRC and demonstrates increased value in CRC diagnosis.
24	**Maric et al.**[19]	2018		+	–	–	IL-$17^{@}$	Yes/S; **DM**	NA	Observations suggest that IL-33 and IL-17 could be potential therapeutic targets.

(*continued on next page*)

Table 1 (*continued*)

SL. No	Authors	Year	Type of CA	IL-33 ↑	IL-33 ↓	NC	Other Biomarkers investigated	Association/ correlation with CPC	Survival outcomes	Clinical implications
								Parameters		
25	**Landskron et al.**[41]	2019		–	–	-$	sST2	Yes/NS	NA	IL-33/ST2 axis likely influences the TME, contributing to invasion and metastasis through activation of desmoplasia.
26	**Chatrabnous et al.**[42]	2019	**PC**	+	–	–	–	Yes/S; **TS**	NA	IL-33 may play a role in the progression of PC.
27	**Liu et al.**[43]	2022	**EAC**	+	–	–	sST2, IL-4, IL-6, IL-10, IL-1β	Yes/S; **TS**	NA	IL-33 is a potential preventive target for EAC.
28	**Wu et al**[44]	2018	**RCC**	+	–	–	–	Yes/S; **TS, LNM**	Yes/S	In RCC, elevated IL-33 expression is linked to TNM stage and inversely associated with prognosis.
29	**Kieler et al.**[45]	2019	**PDAC**	–	–	**	sST2[#], CA-19-9[NS]	NA	Yes/S	*
30	**Belfrage et al.**[47]	2024		–	–	-$	sST2, MLKL, CEA, CA 19-9	NA	NA	IL-33 levels were consistent across all patient groups.
31	**Zeng et al.**[48]	2016	**EC**	+	–	–	IL-31, CEA[NS], CA-125[NS], CA19-9 [NS]	Yes/S; **TS, DI, LNM, DM**	NA	Interleukins (IL-31, IL-33) may serve as useful biomarkers for the prognosis of EC.
32	Sowa **et al.**[49]	2018	**SGT**	+	–	–	sST2, IL-4, IL-10	Yes/S **Ts[@]**	NA	This is the first evidence suggesting that serum IL-33 and its sST2 receptor may be important in the pathology of parotid gland tumors.
33	**Malekzadeh et al.,**[50]	2018		+	–	–	–	Yes/S **TS[@]; Ts[@]**	NA	IL-33 may be proposed as a novel biomarker for differentiating among various types of SGT.
34	**Zare et al.** [51]	2018		+	–	–	–	Yes/S **TS[@]; Ts[@]**	NA	IL-33 may be proposed as a novel biomarker for distinguishing between different types of SGTs.
35	**Musolino et al.**[24]	2013	**HM**	–	+	–	–	Yes/S; **TS[#]**	NA	Targeting cytokines involved in T-cell-dependent activation could disrupt the TME that enables plasma cell survival and proliferation.
36	**Gangemi et al.**[25]	2013		–	+	–	–	NA	NA	This study is the first to show reduced IL-33 levels in patients with PV or ET, indicating that this decrease may contribute to their immune system changes.
37	**Chen et al.**[4]	2014	**Pooled data on CA**	+	–	–	–	Yes/NS	Yes/NS	IL-33 may serve as an important indicator for tumor detection and prognosis.
	Pan et al.[30]	2023	**Pooled data on HCC**	+	–	–	–	Yes/S; **TS, TG, DM, Ts TS[@], VI[@]**	Yes/S	The IL-33/ST2 axis is a valuable predictive and prognostic biomarker for clinical evaluation and may also serve as a potential therapeutic target.
38	**Firouzabadi et al.**[54]	2022	**Opium users ± cancer**	+	–	–	sST2	NA	NA	A decrease in sST2 levels and an increase in IL-33 levels serve as valuable biomarkers for predicting cancer.

AST: Aspartate aminotransferase; ALT: Alanineaminotransferase; AFP: Alpha fetoprotein; Breast cancer; CA: Cancer; CAF: Carcinoma associated fibroblasts; CA 125-Carbohydrate antigen 125; CEA; Carcinoembryonic antigen; CA153: Carbohydrate antigen 153; CNTF: Ciliary neutrophil factor; CPC: Clinicopathologic features; CRC: Colorectal cancer; CRP: C-reactive protein; DD: Duration of disease; DI: Depth of Invasion; DM: Distant Metastasis; EAC: esophageal adenocarcinoma; EC: Endometrial Cancer; ER: Estrogen receptor; ET: essential thrombocythemia; FH: Family history; GC: Gastric cancer; GERD: chronic gastroesophageal reflux disease; γGT: Gamma glutamyl transferase; HCC: Hepatocellular carcinoma; HER 2: Human epidermal growth factor receptor 2; HM: Haematological malignancies; HP: Histopathology; INR: Liver synthesis; LNM: Lymph node metastasis; Ki-67:Tumor proliferation marker; MA: Meta-analysis; MLKL: mixed lineage kinase domain-like protein; MIF: Migration inhibitory factor; MS: Metastasis status; MM: Multiple myeloma; MPN: Myeloproliferative neoplasms; MMP-11: Matrix metalloproteinase 11; NLR: Neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; No: Number; NSCLC: Non-small cell lung carcinoma; NS: Non-significant; PC: Prostrate cancer; PDAC: Pancreatic ductal adenocarcinoma; PDGF-C: Platelet derived growth factor C; PFS: Progression free survival; PR: Progesterone receptor; PV: Polycythemia vera; RCC: Renal cell carcinoma; SGT: Salivary gland tumor; TPSA; Tissue polypeptide specific antigen; TME: Tumor microenvironment; TNM: Tumor size-nodal status-metastasis; TME: Tumor microenvironment; TG: Tumor Grade; Tg: Tumor growth; TL: Tumor location; TS: Tumor Stage; Ts: Tumor size; UL: Uterine Leiomyoma; VI: vascular invasion; VEGF: Vascular endothelial growth factor; Wt: weight.

*No comment.

** No control Group.

@ Significant correlation positive with serum IL-33.

Significant negative correlation with serum IL-33; NA: Not assessed; NS: No significant association/correlation; S: Significant association.

$ No significant difference.

biomarker. Similarly, Bergis et al.[26] investigated IL-33 and sST2 in serum, finding that sST2 were significantly higher in GC subjects compared to those with H. pylori gastritis or HC. Elevated sST2 correlated with lower tumor differentiation, advanced stages, and metastasis. The ratio of IL-33/sST2 effectively distinguished between non-tumor and tumor individuals, indicating its diagnostic potential. Hu et al.[31] investigated the connection between serum IL-33 and progression-free survival (PFS) in patients with advanced GC. They found pre-chemotherapy serum IL-33 was significantly higher than post-chemotherapy and those in HC. A decline in IL-33 levels of over 30.1 % post-chemotherapy was associated with longer PFS and correlated with distant metastasis. Overall, these studies highlight the significance of serum IL-33 and its interaction with other factors in GC prognosis, suggesting that monitoring IL-33 levels could improve patient

Table 2
Studies Investigating soluble ST2 in Cancers and associated Clinical Implications.

SL. No	Authors	Year	Type of CA	sST2 ↑	sST2 ↓	NC	Other Biomarkers investigated	Association/ correlation with CPC	Survival outcomes	Clinical implications
1	**Bergis et al.[26]**	**2016**	**GC**	+	-	-	IL-33[@]	**Yes/S; TS, TS[@], DM[@], DD[@]**	Yes/NS	sST2 is linked to advanced stage, MD, DD. The IL-33/sST2 ratio could provide a promising new method for identifying GC patients.
2	**Xu et al.[16]**	**2018**	**NSCLC**	+	-	-	IL-33, IL-4	**NA**	NA	The IL-33/ST2 pathway in the microenvironment of NSCLC promotes a Th2, which may support Tg.
3	**Pang et al.[27]**	**2020**		+	-	-	IL-33, IL-17A, IFNγ, IL-10, IL-4	**NA**	NA	Elevated levels of IL-33 and sST2 in patients with NSCLC may lead to an imbalance between Th1 and Th2 cytokines.
4	**Lu et al.[28]**	**2014**	**BC**	+	-	-	IL-33, ER, PR, HER2, Ki-67, VGEF[@]	**Yes/S; Age, TS, Ts, LNM, HP, Ki-67**	Yes/NS	Serum sST2 levels are elevated in ER-positive BC and are significantly linked to factors that suggest a poor prognosis.
5	**Yang et al.[29]**	**2015**		+	-	-	IL-33, VEGF[@], MMP-11[@], PDGF-C[@].	**NA**	NA	IL-33 and sST2 have the potential to act as non-invasive diagnostic markers for BC.
6	**Chen et al.[36]**	**2023**		-	-	-**	D- Dimer, CA153, CA125, TPSA, CEA, ER, PR, HER2, Ki-67	**Yes/S; Cardiotoxicity, TS**	Yes/S	Serum sST2 may be valuable for diagnosing TNBC and assessing the prognosis of advanced BC.
7	**Bergis et al.[6]**	2013	**HCC**	+	-	-	IL-33[NS], AFP[@], ALT, AST[@], INR[@], Bilirubin, CRP[@], Na, Creatinine	**Yes/S; TS**	Yes/S	Serum sST2 concentration is associated with OS in HCC indicating its potential as a new prognostic marker.
8	**Wang et al.[22]**	2022		-	-	+	IL-33, Perforin, Granzyme B	**NA**	NA	*
9	**Pan et al.[30]**	2023		+	-	-	IL-33	**NA**	NA	ST2 mRNA and serum levels were significantly elevated in HCC patients compared to HC.
10	**Yasen et al.[38]**	**2024**		+	-	-	IL-33, MI F[@]	**Yes/S; Ts, TG, LNM, TS**	NA	High sST2 levels were associated with aggressive clinicopathologic traits, suggesting IL-33/ST2 signaling as a potential diagnostic biomarker and therapeutic target for ICC.
11	**Tang X et al.[39]**	**2024**		+	-	-	AFP	**Yes/NS**	NA	sST2 demonstrated diagnostic performance comparable to AFP, highlighting its potential as a promising HCC biomarker. Combining sST2 with AFP enhanced diagnostic accuracy.
12	**O'Donnell et al.[23]**	2016	**CRC**	-	-	+	IL-33	**NA**	NA	ST2L may have a potential antitumorigenic role in colon cancer, with the IL-33/ST2 signalling axis possibly providing protective effects against colon carcinogenesis.
13	**Akimoto et al.[40]**	2016		-	-	**	–	**Yes/S; TS, Ts**	NA	IL-33/ST2L axis may serve as a potential therapeutic target. Recombinant sST2 could be used as an anti-tumorigenic and anti-metastatic agent.
14	**Landskron et al.[41]**	2019		-	-	+	IL-33	**Yes/NS**	NA	The IL-33/ST2 interaction in the TME, likely promotes invasion and metastasis by activating desmoplasia.
15	**Liu et al.[43]**	2022	**EAC**	-	+	-	IL-33, IL-4, IL-6, IL-10, IL-1β	**Yes/NS**	NA	IL-33 may serve as a potential preventive target for EAC.
16	**Kieler et al.[45]**	2019	**PDAC**	-	-	**	IL-33[#], CA-19-9[NS]	**NA**	NA	Elevated levels of sST2 negatively affect survival.
17	**Torrente-Rodríguez et al.[46]**	2021		+	-	-	-	**Yes/NS**	NA	No significant differences between immune platform and ELISA method. sST2 levels showed a significant negative association with median OS rates.
18	**Belfrage et al.[47]**	2024		+	-	-	**MLKL, IL-33, CA-19–9[@], CEA[@]**	**NA**	NA	Elevated sST2 levels are associated with pancreatic diseases.
19	**Sowa et al.[49]**	2018	**SGT**	+	-	-	IL-33, IL-4, IL-10	Yes/S; **Ts[@]**	NA	Serum IL-33 and sST2 may play significant roles in the pathology of parotid gland tumors.
20	**Aarstad et al.[52]**	2020	**HNSCC**			**	IL-6, IL-6Rα, Il-31, IL-27, gp130, CNTF, Oncostatin M, TNFα, IL-1RA, CRP	**Yes/NS**	Yes/NS	Serum IL33Rα levels did not show an association with prognosis.
21	**Aarstad et al.[53]**	2021				**	IL-6, IL-27, IL-31, CNTF, OSM, gp130, IL-6Rα, IL-1RA	**Yes/NS**	Yes/S	Serum levels of IL-6, gp130, IL-1RA, and ST2 may serve as prognostic markers in

(*continued on next page*)

Table 2 (*continued*)

SL. No	Authors	Year	Type of CA	sST2 ↑	sST2 ↓	NC	Other Biomarkers investigated	Association/ correlation with CPC	Survival outcomes	Clinical implications
22	**Firouzabadi et al.**[54]	2022	**Opium users ± Cancer**	-	+	-	IL-33	**NA**	NA	patients with HNSCC, suggesting their potential as biomarkers in cancer. The reduction in sST2 levels and an elevation in IL-33 levels are important biomarkers for predicting cancer.

AST: Aspartate aminotransferase; ALT: Alanineaminotransferase; AFP: Alpha fetoprotein; Breast cancer; CA: Cancer; CAF: Carcinoma associated fibroblasts; CA 125-Carbohydrate antigen 125; CEA; Carcinoembryonic antigen; CA153: Carbohydrate antigen 153; CNTF: Ciliary neutrophic factor; CPC: Clinicopathologic features; CRC: Colorectal cancer; CRP: C-reactive protein; DD: Duration of disease; DI: Depth of Invasion; DM: Distant Metastasis; EAC: esophageal adenocarcinoma; EC: Endometrial Cancer; ER: Estrogen receptor; ET: essential thrombocythemia; FH: Family history; GC: Gastric cancer; GERD: chronic gastroesophageal reflux disease; γGT: Gamma glutamyl transferase; HCC: Hepatocellular carcinoma; HER 2: Human epidermal growth factor receptor 2; HM: Haematological malignancies; HP: Histopathology; IL6Rα- IL6 receptor alpha; IL1RA: IL1R antagonist (A) INR: Liver synthesis; LNM: Lymph node metastasis; Ki-67:Tumor proliferation marker; MA: Meta-analysis; MS: Metastasis status; MLKL: mixed lineage kinase domain-like protein; MM: Multiple myeloma; MPN: Myeloproliferative neoplasms; NLR: Neutrophil lymphocyte ratio; No: Number; NSCLC: Non-small cell lung carcinoma; NS: Non-significant; OSM: Oncostatin M; OS:Overall survival; PDAC: Pancreatic ductal adenocarcinoma; PC: Prostrate cancer; PR: Progesterone receptor; PFS: Progression free survival; PLR: platelet lymphocyte ratio; PV: Polycythemia vera; RCC: Renal cell carcinoma; SGT: Salivary gland tumor; Tg: Tumor growth; Th2:T helper cell 2 response; TPSA; Tissue polypeptide specific antigen; TME: Tumor microenvironment; TNM: Tumor size-nodal status-metastasis; TNF α: Tumor necrosis factor alpha; TNBC: Triple-negative breast cancer; TME: Tumor microenvironment; TG: Tumor grade; TL: Tumor location; TS: Tumor Stage; Ts: Tumor size; UL: Uterine Leiomyoma; VI: vascular invasion; Wt: weight.

*No comment.

** No control Group.

@ Significant correlation positive with serum IL-33.

 # Significant negative correlation with serum IL-33; NA: Not assessed; NS: No significant association/correlation S: Significant association.

management and treatment outcomes.

4.3. Serum IL-33 and sST2 in lung cancer (LC)

The functions of various angiogenesis-related factors like IL-20, IL-29, IL-33, and Galectin 3 in LC are still being clarified. Naumnik et al.[32] measured serum levels of these interleukins in 45 patients with non-small cell lung cancer (NSCLC), 8 with hypersensitivity pneumonitis (HP), 15 with sarcoidosis, and 15 HC using ELISA. Results showed that IL-20 was highest in NSCLC, while Galectin 3 peaked in HP. IL-29 was most elevated in HP, and IL-33 levels varied, being lowest in HC and highest in HP. Notably, IL-33 and IL-29 were reduced in NSCLC patients with metastatic disease, though these markers did not significantly differ based on therapy response, with a noted correlation between IL-33 and Galectin 3. Overall, while serum levels of these markers were elevated in patients with NSCLC compared to HC, their clinical utility remains limited. Further research by Naumnik et al.[33] on IL-33, IL-31, IL-29, and IL-27 in LC revealed that serum IL-29 was significantly higher in NSCLC compared to the sarcoidosis patients, while IL-33, IL-31, and IL-27 showed no significant differences.

The function of IL-33 in tumor immunity was explored by Hu et al.[3] and Petrovic et al.[15] They found that serum IL-33 was markedly higher in NSCLC group compared to benign lung diseases group and HC. Serum IL-33 has been identified as a robust diagnostic marker and an independent prognostic factor for NSCLC, especially in its advanced stages. In contrast, Kim et al.[20] observed that IL-33 levels were significantly reduced in LC subjects than in HC, decreasing progressively with disease stage. In conclusion, IL-33 levels are inversely linked to the progression of LC, with the decrease likely attributed to reduced lung volume, which impacts the bronchial epithelium and vascular endothelium—both key sources of IL-33. Within the cancer cohort, IL-33 decreased in relation to cancer stage.

Xu et al.[16] studied the IL-33 and ST2 signaling in NSCLC, examining their interplay between inflammation, immunity, and cancer. They analyzed samples from patients and measured serum IL-33, ST2, Interferon (IFN)-γ, and IL-4 levels using ELISA and WB. The results showed that IL-4, IL-33, and ST2 were significantly elevated in both tumor tissues and serum compared to HC. In the NSCLC microenvironment, the IL-33/ST2 signaling stimulates the Th2 immune activity, which may contribute to tumor growth. Pang et al.[27] observed increased protein levels and mRNA expression of IL-33 and ST2 in tissues of NSCLC, alongside increased serum levels of IL-33, sST2, IL-17A, IL-10, and IL-4 with reduced IFN-γ. The positive correlation of IL-33 with IL-4 and IL-10, coupled with its negative correlation with IFN-γ, suggests a Th1/Th2 cytokine imbalance in NSCLC.

4.4. Serum IL-33 and sST2 in breast cancer (BC)

Research on IL-33 has highlighted its potential role in BC progression. Liu et al.[34] noted that serum IL-33 levels were nearly doubled in the BC group compared to those with benign breast diseases, with significantly higher levels in the estrogen receptor (ER) - positive BC group. Increased IL-33 was connected with a family history of malignancies but showed no correlation with factors like age, menopausal status, or tumor characteristics. Lu et al.[28] investigated the association between serum IL-33, sST2, and vascular endothelial growth factor (VEGF) and CPC in BC. They found significantly elevated serum levels of these markers in BC patients compared to HC. In ER-positive patients, sST2 correlated with age, tumor size, clinical stage, histological type, and Ki-67 status, and serum IL-33 and sST2 in BC significantly correlated with VEGF. Post-surgery serum levels of IL-33, sST2, and VEGF decreased; however, they showed no association with disease-free survival (DFS) or overall survival (OS). The investigators concluded that elevated sST2 in ER-positive patients is linked to poor prognostic indicators, indicating its role in disease pathogenesis. Yang et al.[29] also observed increased serum levels of IL-33 and sST2 in individuals with BC, accompanied by elevated VEGF, platelet-derived growth factor-C (PDGF-C), and metalloproteinase-11 (MMP-11). Serum IL-33 and sST2 showed positive correlations with VEGF, PDGF-C, and MMP-11, suggesting their potential as non-invasive diagnostic markers for BC.

Haghbin et al.[35] analyzed IL-33 levels in individuals with BC and idiopathic granulomatous mastitis (IGM) compared to HC. They observed no significant variation in serum IL-33 levels with respect to age, marital status, BMI, or menopausal status. However, IL-33 levels were substantially elevated in both the BC and IGM groups compared to HC, with no considerable differences observed between the two patient groups. The investigators concluded that while IL-33 is a significant marker distinguishing IGM and BC patients from HC, it is not reliable for diagnosing or differentiating between BC and IGM. Serum IL-33 may serve as an important marker for BC, indicating its association with malignancy and potential involvement in tumor progression and metastasis.

Chen et al.[36] examined sST2 expression in BC patients across various molecular subtypes and assessed its prognostic value in advanced BC. They found that serum sST2 levels did not significantly differ among different pathological and molecular types, including subgroups defined by ER, HER2, Ki-67, and progesterone receptor (PR). The only significant difference was observed in the cardiotoxicity group. Importantly, patients with high sST2 levels had significantly poorer survival compared to those with normal levels, indicating that sST2 is not only relevant for cardiac injury assessment but also serves as a prognostic marker for advanced BC, independent of clinical stage and cardiotoxicity.

4.5. Serum IL-33 and sST2 in hepatocellular carcinoma (HCC)

HCC, the leading type of primary liver cancer, frequently arises in the context of liver cirrhosis and is linked to unfavorable outcomes.[6] Zhang et al.[17] investigated the role of cytokines in the pathogenesis of HCC and their clinical significance. They measured IL-33 in normal liver tissues and tumors as well as serum levels of IL-33, IFN-α, and IFN-γ in individuals with HCC and HC. Their findings revealed markedly higher serum levels of these cytokines in subjects with HCC, especially in those with metastasis, suggesting that IL-33 could serve as a biomarker for tumor growth and spread. Askoura et al.[37] examined IL-33, IL-25, and IL-17 in chronic hepatitis C and HCC patients, finding elevated IL-25 in HCC and higher IL-33 and IL-17 levels in both chronic hepatitis C and HCC compared to HC. IL-33 levels increased with liver fibrosis and viral load, indicating its role in liver inflammation, while IL-25 and IL-17 may signal the transition to HCC.

Recent research suggests that the Th2 cytokine IL-33 may contribute to cancer development. IL-33 interacts with its receptor and sST2, which has regulatory functions, but the relationship of IL-33, sST2, liver disease progression, and survival in cirrhosis and HCC is not well understood. Bergis et al.[6] found no notable variations in IL-33 levels among individuals with HCC, cirrhosis, or HC, nor did it correlate with OS or disease progression. In contrast, sST2 levels were significantly increased in both groups, correlating with survival in HCC patients, indicating that sST2 could serve as an important prognostic marker. Even Pan et al.[30] studied 565 HCC subjects and 561 controls, assessing serum IL-33 and sST2. They found increased sST2 levels in HCC subjects, but IL-33 levels did not remarkably differ, aligning with other investigations in the field.

Shen et al.[21] analyzed chemokines and cytokines in the blood of HCC subjects and identified significantly increased levels of IL-1β, IL-6, IL-10, IL-17A, IL-22, and IL-25, alongside reduced IL-4 and IL-33. They proposed an eight-cytokine signature for HCC detection. Wang et al.[21] studied IL-33 and ST2 in HCC patients, finding reduced IL-33 levels and mRNA expression in peripheral blood mononuclear cells compared to HC. No notable differences were observed in ST2 levels or expression between the two groups, and the proportions of $CD8^+$ T cells did not correlate with IL-33 or ST2 levels. The researchers proposed that the reduced IL-33 in HCC patients may hinder $CD8^+$ T cell cytotoxicity, suggesting a possible avenue for therapeutic intervention.

Yasen et al.[38] explored IL-33/ST2 signaling in intrahepatic cholangiocarcinoma (ICC) and its association with macrophage diversity and clinicopathologic features. Tumor tissues showed increased CD68-positive cells and higher expression of both M1 and M2 macrophage markers, with M2 macrophages being predominant. Plasma levels of IL-33, ST2, and Migration inhibitory factor (MIF) were elevated in ICC patients and correlated with tumor size, lymph node metastasis (LNM), TNM stage, and differentiation. IL-33 and ST2 expression in tumor tissues was linked to both macrophage phenotypes. IL-33 was associated with tumor size, LNM, and TNM stage, while ST2 and MIF correlated with tumor size and TNM stage. IL-33/ST2 signaling was positively related to macrophage heterogeneity and aggressive CPC, suggesting potential as diagnostic biomarkers and therapeutic targets for ICC.

Tang et al.[39] explored sST2 as a serum marker for diagnosing HCC. They found that sST2 levels were significantly higher in the HCC group compared to the chronic Hepatitis B (CHB) and HC groups. No significant correlations were found between sST2 and other clinical indicators in the HCC group. The diagnostic performance of sST2 was similar to Alpha-Fetoprotein (AFP), suggesting its potential as a promising biomarker for HCC detection The combination of sST2 and AFP enhanced the diagnostic accuracy for HCC. The study emphasizes the potential of sST2 as a blood-based marker for HCC detection and the improved diagnostic performance when combined with AFP in HCC screening, indicating that further research could pave the way for new strategies in managing HCC.

4.6. Serum IL-33 and sST2 in colorectal cancer (CRC)

The function of cytokine IL-33 and its receptor ST2 in colon cancer continues to be uncertain, despite the known link between inflammation and cancer. O'Donnell et al.[23] investigated IL-33 and its receptor isoforms in this setting. Serum levels of IL-33 and sST2 were measured using ELISA, while IL-33 and ST2 expression in tissue was evaluated through IHC, WB, and qRT- PCR. This study found that CRC patients had slightly lower serum IL-33 levels than HC, with no significant changes in sST2. Notably, colon tumors displayed reduced ST2L expression relative to adjacent non-tumor tissue, and this reduction became more pronounced as the tumor grade advanced. These findings imply that ST2L may play a potential antitumorigenic role in colon cancer, potentially mediated by immune cell infiltration, especially macrophages and $CD8^+$ T cells. Modulating ST2L could provide therapeutic benefits, suggesting that the IL-33/ST2 axis may play a protective role in colon carcinogenesis.

Akimoto et al.[40] discovered that sST2 is inversely related to CRC malignancy. Specifically, sST2 levels are reduced in high-metastatic CRC cells compared to low-metastatic ones. Silencing sST2 in low-metastatic cells promotes angiogenesis, tumor growth, and metastasis, whereas overexpressing sST2 in high-metastatic cells inhibits these processes. At the molecular level, sST2 suppresses IL-33-induced angiogenesis, macrophage infiltration, M2a polarization, and T-cell activation. Overall, sST2 inhibits CRC growth and metastasis by targeting the TME, highlighting the IL-33/ST2 axis as a potential treatment strategy in CRC.

Tumor immunotherapy shows promise globally, with IL-33 emerging as a key player in tumor immunity as a danger signal from damaged cells. Xie et al.[18] examined IL-33 expression in CRC and its association with clinical features and prognosis. They found that IL-33 positivity was considerably reduced in tumors than in peritumoral tissues. Serum IL-33 expression was higher in moderately or poorly differentiated CRC compared to well-differentiated cases, and subjects with colon cancer had elevated serum IL-33 activity compared to those with rectal cancer. This study suggested that combining serum IL-33 with Carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9) could improve CRC diagnostic accuracy. The researchers concluded that IL-33 is linked to tumor progression in CRC and may serve as an important diagnostic tool.

IL-33 is crucial in the TME and CRC progression. CRC is frequently diagnosed at later stages, emphasizing the need for novel diagnostic markers. Maric et al.[19] investigated systemic and fecal IL-17 and IL-33 expression in CRC, exploring their relationship with clinicopathologic features. They observed increased serum IL-33 and fecal IL-17 activity in patients with lung or liver metastases, as well as peritoneal carcinomatosis. A strong positive relation between IL-33 and IL-17 levels was observed in both serum and feces. The researchers suggested that higher concentrations of these cytokines may indicate malignant progression in CRC patients with poorly differentiated tumors and metastasis, implying a poorer prognosis. These findings suggest that IL-33 and IL-17 could be potential therapeutic targets.

Landskron et al.[41] investigate the relation between the IL-33/ST2 pathway and desmoplasia, a key factor associated with metastasis in CRC. The study finds that elevated IL-33 levels correlate with increased desmoplastic response in CRC, which is linked to tumor aggressiveness

and metastasis. Conversely, higher sST2 levels appear to be protective, suggesting a potential role in mitigating tumor progression. Overall, the findings indicate that the IL-33/sST2 axis may serve as an important indicator for assessing desmoplasia and metastatic potential in CRC, providing insights for potential therapeutic strategies.

4.7. Serum IL-33 and sST2 prostrate cancer (PC)

Prostate cancer (PC) is one of the most prevalent malignancies in men, with its progression often driven by inflammatory processes. Inflammation can foster an environment conducive to tumor development and metastasis. IL-33 is a cytokine that exhibits both inflammatory and anti-inflammatory properties, making its role in the cancer complex. In a study by Chatrabanous et al.,[42] blood samples from recently diagnosed PC cases were analyzed alongside age-matched HC. The researchers found substantially increased serum IL-33 levels in PC, especially those with advanced disease stages, indicating a correlation between IL-33 activity and disease progression. Increased levels of IL-33 may influence the TME by activating type 2 innate lymphoid cells and promoting M2 macrophage polarization, which supports tissue repair, angiogenesis, and tumor progression. IL-33 also triggers the release of pro-inflammatory cytokines and chemokines, thereby further promoting tumor progression and spread. Its link to increased cellular proliferation, migration, and invasion plays a role in the aggressive behavior of advanced PC. The association between elevated serum IL-33 levels and advanced disease stages indicates its potential as a biomarker for tracking disease progression and assessing treatment response. Modulating the IL-33/ST2 signaling pathway could provide new therapeutic strategies, shifting the IR toward a more anti-tumor profile and potentially slowing disease progression.

4.8. Serum IL-33 and sST2 in esophageal adenocarcinoma (EAC)

The progression from long-standing gastroesophageal reflux disease (GERD) to Barrett's esophagus and ultimately to EAC involves inflammatory-driven neoplastic changes, with IL-33 identified as a key factor. Liu et al.[43] analyzed IL-33 expression using PCR, WB, IHC, and ELISA. Their findings showed that IL-33 levels increased progressively from GERD to EAC, with the protein initially exported from the nucleus into the cytoplasm and then into the surrounding environment. IL-33 stimulates the proliferation, epithelial-mesenchymal transition (EMT), migration, and invasion of EAC cells by interacting with the ST2 receptor, which also increases IL-6 secretion. This study was the first to clarify IL-33's role in the inflammatory transformation associated with EAC, revealing that serum IL-33 activity rises with advancing disease stages, while sST2 levels are undetectable. These findings indicate that IL-33 may serve as a promising candidate for preventive strategies against EAC. Overall, IL-33's role in the progression of EAC underscores its promise as both a biomarker and treatment target in managing this disease.

4.9. Serum IL-33 and sST2 in renal cell carcinoma (RCC)

IL-33 has an unclear role in RCC. A recent study by Wu et al.[44] found significantly increased serum IL-33 levels in patients with RCC compared to HC, correlating with advanced TNM stage and poorer patient prognosis. The results indicate that increased IL-33 may play a role in tumor growth and metastasis, emphasizing its potential as a biomarker for disease severity. The researchers propose that modulating the IL-33/ST2 and JNK axis could provide promising therapeutic strategies for RCC by disrupting mechanisms that promote tumor growth and immune evasion.

4.10. Serum IL-33 and sST2 in pancreatic ductal adenocarcinoma (PDAC)

Kieler et al.[45] investigated IL-33 and sST2 as potential prognostic markers in individuals with metastatic and locally advanced PDAC. They assessed IL-33 and sST2 levels in twenty PDAC cases prior to initiating systemic chemotherapy and examined their correlation with clinical outcomes. Kaplan-Meier and multivariable Cox proportional hazards model analyses revealed that increased sST2 levels were notably associated with reduced survival in individuals undergoing chemotherapy for advanced PDAC. This research is the first to examine circulating IL-33 and sST2 in this context, suggesting that high sST2 levels negatively impact survival. Torrente-Rodríguez et al.[46] also found that PDAC patients had higher average sST2 concentrations, with two patients showing elevated levels suffering from high-grade metastatic tumors and poorer prognoses. These results reinforce Kieler et al.'s findings of a notable negative correlation between sST2 levels and median OS rates.[45]

Belfrage et al.[47] compared plasma levels of necroptosis-related markers [(Mixed lineage kinase domain like) MLKL, IL-33, and sST2] in patients with chronic pancreatitis (CP), PDAC, and HC to assess their diagnostic and prognostic value. Plasma MLKL was lower in CP patients compared to other groups. sST2 levels were significantly lower in HC than in the other groups and in PDAC patients with a soft pancreas compared to those with a non-soft pancreas. In Lewis antigen-positive PDAC, sST2 showed positive correlations with CA19-9 and CEA. Elevated sST2 levels are linked to pancreatic diseases.

4.11. Serum IL-33 and sST2 in Endometrial Cancer (EC)

Previous research has indicated that IL-33 and IL-31 may serve as promising indicators in cancer. Zeng et al.[48] aimed to assess their prognostic roles in EC patients using ELISA kits targeted for IL-33 and IL-31, while serum levels of carbohydrate antigen −125 (CA-125), CEA, CA 19–9 were assessed using a chemiluminescence immunoassay. Both IL-33 and IL-31 levels were substantially higher in patients compared to HC and were associated with clinicopathologic parameters such as tumor stage, lymph node metastasis, distant metastasis, and depth of invasion. The sensitivity and specificity of IL-33 and IL-31 surpassed those of traditional tumor markers, whether individually or in combination with clinical indicators. This study is the first to suggest a potential link between IL-33 and IL-31 and EC, indicating that these interleukins may be valuable prognostic biomarkers.

4.12. Serum IL-33 and sST2 in salivary gland tumors (SGT)

Serum IL-33 and ST2 are implicated in SGT, with elevated levels potentially associated with tumor progression and inflammatory responses. Sowa et al.[49] assessed serum levels of IL-33 and sST2 in individuals with various types of parotid gland tumors, including pleomorphic adenoma (PA), Warthin's tumor (WT), myoepithelioma, and acinic cell carcinoma (ACC). They found that serum IL-33 was markedly increased in these patients, while sST2 was notably higher in those with PA and ACC compared to HC. This study highlights the potential role of serum IL-33 and sST2 in the pathology of parotid gland tumors, suggesting that they could serve as biomarkers. This study emphasizes the possible role of serum IL-33 and sST2 in the pathology of parotid gland tumors, suggesting that they could serve as biomarkers.

Furthermore, few investigations measured serum IL-33 in subjects with benign and malignant SGT. Results showed raised IL-33 levels in subjects with malignant SGTs, such as ACC, mucoepidermoid carcinoma (MEC), and malignancies of mixed type (MMT), compared to those with benign tumors and HC. Additionally, a significant relation was found between IL-33 levels and tumor size and stage, indicating that higher levels of this cytokine may reflect more advanced disease. This increase in IL-33 may be connected to a Th2 IR characterized by IL-4 and IL-5

production, which inhibits Th1 cell development and promotes regulatory T cells, ultimately supporting the growth of SGTs. The findings indicate that IL-33 could be integral in creating an immune environment that supports the progression of SGT.[50,51]

4.13. Serum IL-33 and sST2 in head and neck squamous cell carcinoma (HNSCC)

Aarstad et al.[52] studied the pre-treatment inflammatory cytokine profile in 144 subjects with locally advanced HNSCC. They measured serum levels of various cytokines, including IL-1 subfamily members, IL-6 family mediators, and TNFα. While IL-33 is recognized as an acute-phase cytokine, no association was found between systemic IL-33Rα levels and prognosis. In another study, researchers evaluated serum IL-6, glycoprotein 130 (gp130), IL-1RA, and ST2 as prognostic markers in HNSCC. They found that both IL-6 and gp130 were significant predictors of survival, with higher levels associated with worse outcomes, a finding supported by a multivariate Cox model. IL-1RA also predicted survival across the entire cohort, maintaining significance in multivariate analysis. For HPV-negative patients, ST2 indicated survival trends after adjusting for relevant covariates. Other soluble markers did not predict survival. These results suggest that serum IL-6, gp130, IL-1RA, and ST2 have prognostic roles in HNSCC and could serve as potential indicators in cancer management.[53]

Although the involvement of serum IL-33 in HNSCC is largely unexplored, sST2 has attracted some attention in preliminary studies. Existing research primarily focuses on IL-33 and ST2 expression in tumor tissues, revealing intriguing correlations with tumor characteristics and IR.[12,55–57] However, the lack of comprehensive investigations into serum IL-33 in HNSCC presents a significant gap in our understanding of its potential as a biomarker. Given the critical roles these molecules play in immune modulation and TME dynamics, further exploration is warranted. Understanding the serum levels of IL-33 could provide insights into systemic IR and the potential for using this biomarker in clinical practice. Additionally, expanding studies on sST2 in the context of HNSCC may reveal its prognostic value and therapeutic implications. Overall, this area of research is ripe for further inquiry, as elucidating the functions of serum IL-33 and sST2 could lead to improved diagnostic tools, better prognostic assessments, and novel therapeutic strategies in HNSCC.

4.14. Serum IL-33 and sST2 in hematological malignancies (HM)

Recent research highlights the importance of serum IL-33 in HM, as well as its potential impact on tumor biology and IR. Musolino et al.[24] evaluated IL-33 levels in 44 multiple myeloma (MM) patients and 13 individuals with monoclonal gammopathy of undetermined significance (MGUS). They found detectable IL-33 levels in 23 MM patients and 8 MGUS patients, with significantly lower levels in MM compared to both MGUS and HC. An inverse relationship was observed between IL-33 levels and disease stage in MM, suggesting its role in immune system changes, particularly as cell-mediated immunity declines in advanced HM. Gangemi et al.[25] investigated IL-33 levels in individuals with polycythemia vera (PV) and essential thrombocythemia (ET), finding that IL-33 levels were significantly lower in these patients compared to HC. This study is the first to document decreased IL-33 in PV and ET, reflecting trends seen in other HMs. The decline in IL-33 may play a role in immune system dysfunction, including changes in T lymphocyte subsets that are characteristic of chronic myeloproliferative neoplasms.

Serum IL-33 plays a significant role in HM, with studies indicating decreased levels in conditions like MM, PV, and ET.[24,25] Lower IL-33 concentrations correlate with advanced disease stages and may reflect immune system changes, including suppressed cell-mediated immunity. In PV and ET, reduced IL-33 levels are linked to immune abnormalities and thrombotic complications.

5. Meta-analysis of serum IL-33 and sST2 in cancer

IL-33 is a versatile cytokine with complex roles, yet its clinicopathological and prognostic significance in HCC remains contested. To investigate this, Pan et al.[30] conducted a meta-analysis. The analysis revealed that at the tumor tissue level, IL-33 expression showed a positive correlation with size, stage, grade, and metastasis. At the serum level, elevated IL-33 was associated with a higher cancer risk and correlated with advanced disease progression and vascular invasion. The IL-33/ST2 signaling holds promise as a predictive and prognostic indicator in clinical assessments and could offer a potential therapeutic strategy.

Chen et al.'s[4] meta-analysis explores the link between serum IL-33 levels and tumor progression across different cancers. Findings demonstrate a significant association between increased serum IL-33 levels and the presence of tumors, implying that IL-33 may be involved in tumor development. The analysis also emphasizes the potential of IL-33 as an indicator for cancer detection and outcomes.

6. Serum IL-33 and sST2 in opium users

Firouzabadi et al.[54] investigated IL-33 and sST2 levels as potential cancer biomarkers in opium users. They found significantly higher serum IL-33 levels and lower sST2 levels in opium users compared to healthy controls. Among opium users with cancer, IL-33 levels were notably elevated, while sST2 levels were lower than in cancer-free individuals. The decline in sST2 and the rise in IL-33 suggest their potential as biomarkers for predicting cancer, especially in opium users, indicating their promise for early cancer detection.

7. Serum IL-33 and sST2 as potential biomarkers in cancer

Biochemical markers, alone or combined with other diagnostic tools, are crucial for diagnosing, treating, and monitoring diseases. They offer non-invasive insights into prognosis, disease progression, and the risk of life-threatening complications.[58] Serum IL-33 and sST2 are emerging biomarkers that have shown promise in improving the detection, prognosis, and monitoring of various cancers. These biomarkers offer distinct advantages compared to traditional biomarkers such as CA-125, CEA, CA 19–9 or AFP, which are commonly used in oncology for specific cancers.[2,6,18,45,47,48]

Identifying markers for early diagnosis and risk prediction is a primary goal in medicine. This review examines the literature on serum IL-33 and sST2, focusing on their roles as diagnostic, prognostic, or predictive markers across different cancers. Based on the data summarized in Table 1, serum IL-33 has significant implications for cancers originating from the breast, lung, gastric, liver, colorectal, prostate, esophageal, renal, endometrial, and salivary glands. IL-33 has emerged as a promising biomarker for tumor detection, prognosis, and therapeutic response in various cancers.[11] While it is often linked to poor prognosis[2,3,15,17–19,31,34,38,42,48,49] in some cases, IL-33 acts as a tumor suppressor by triggering an immune response.[20–25] IL-33 behaves as a tumor suppressor by inducing an immune response. In terms of negative prognosis, high levels of IL-33 were detected in the serum and tumors of patients with GC[2,31], HCC[17,38], NSCLC[3,15], CRC[18,19], PC[42], EAC[43], RCC[44], EC[48], SGT[49], HNSCC[12,55–57], and BC[34], when compared to corresponding healthy controls.[11]

Out of thirty-eight reports, twenty-six indicated that serum IL-33 was significantly raised in cancer compared to HC. Additionally, twenty-two of twenty-six studies that examined serum IL-33 in relation to clinicopathologic characteristics found a significant association, and in twelve studies assessing serum IL-33 and survival, seven reported a meaningful link. IL-33 has emerged as a promising biomarker across various cancers, showing potential for both diagnosis and prognosis. For example, IL-33 may help forecast prognosis in GC and demonstrates strong diagnostic and prognostic value in NSCLC, independent of treatment.[2,3]

In BC, IL-33 is linked to immune suppression, disease progression, and metastasis, and it correlates with indicators of poor prognosis.[34] Elevated IL-33 levels have been associated with poor prognosis in cancers like breast and lung. It is suggested that IL-33 plays a role in immune evasion by promoting tumor-associated inflammation, which contributes to tumor progression and metastasis.[3,15,34] IL-33 also appears effective in tracking growth and metastasis in HCC.[17] In CRC, combining IL-33 with other markers like CEA and CA19–9 may improve diagnostic accuracy, as IL-33 levels correlate with tumor progression.[18] Similarly, IL-33 has been linked to disease progression in PC, while overexpression during the GERD-to-EAC transition suggests it as a preventive target.[42,43] In RCC, high IL-33 expression correlates with advanced TNM stage and poor prognosis, indicating that targeting the IL-33/ST2 axis might provide therapeutic benefits.[44]

Research indicates that IL-33 has increased expression in a variety of cancers, such as BC, NSCLC, and CRC.[3,15,18,19,34] However, the sensitivity of IL-33 as a standalone biomarker can be relatively low in some cancers, especially when used for early detection.[6,32,45,47] In some cases, IL-33 may not be specific enough for individual cancers, as it can also be upregulated in non-cancerous inflammatory conditions.[59] IL-33 is less specific than some other biomarkers like CA-125 for ovarian cancer. Elevated IL-33 levels can occur in inflammatory diseases (e.g., rheumatoid arthritis) and cancers, reducing its specificity and limiting its use as a diagnostic biomarker in clinical practice.[8,59]

Table 2 highlights sST2 as a key biomarker in cancers such as BC, NSCLC, GC, HCC, and PDAC. Of twenty-two studies, twelve reported significantly elevated sST2 levels in cancer compared to HC. seven of thirteen studies examining the relationship between sST2 and CPC found significant associations, and three of six studies analyzing survival outcomes found meaningful links. sST2 demonstrates potential as a diagnostic and prognostic marker across various cancers. In GC, sST2 is linked with advanced stages and extended disease duration, and the ratio of IL-33/sST2 may assist in identifying GC patients.[26] Elevated sST2 levels correlate with poor prognosis, reflecting the cancer's ability to induce chronic inflammation.[28] Elevated sST2 is associated with tumor aggressiveness, advanced stages, and metastasis.[6,26,36,38] In BC, sST2 levels have been shown to predict recurrence and survival.[36] Similarly, elevated sST2 levels in NSCLC are associated with worse outcomes and lower response rates to therapy.[16,27] In HCC, serum sST2 is linked to OS.[6] In CRC, sST2 may inhibit tumor growth and spread by modulating the TME, highlighting the IL-33/ST2 pathway as a potential treatment target. Recombinant sST2 could function as an anti-tumorigenic agent.[23,40] In PDAC elevated levels of sST2 negatively affect survival[45,46]

sST2 has been found to correlate with tumor burden and inflammation in cancers such as GC, NSCLC, BC, HCC and PDAC.[6,16,26–28,30,46,47] It can be a more sensitive marker in detecting ongoing tumor progression compared to traditional markers like CEA or CA-19-9.[6,28,36,45,47] In some studies, sST2 is used alongside other biomarkers to improve detection sensitivity. sST2 demonstrated diagnostic performance comparable to AFP, highlighting its potential as a promising HCC biomarker. Combining sST2 with AFP enhanced diagnostic accuracy.[39] sST2's specificity can be high in certain cancers. It is more specific than IL-33 because it directly correlates with the tumor's immune response via the IL-33/ST2 axis. However, since sST2 levels may also be influenced by other chronic inflammatory conditions, caution must be taken in interpreting its levels.[58] sST2 has shown considerable promise as a prognostic biomarker in cancers like BC, HCC, NSCLC.[6,16,27,28,39,29,38]

The combination of IL-33 and sST2 may offer higher sensitivity and specificity compared to each biomarker alone. Studies show that measuring both markers together may improve the ability to predict tumor recurrence, response to treatment, and survival outcomes.[16,27–29,38,49] For instance, in breast cancer, both elevated IL-33 and sST2 levels are associated with poor prognosis, and their combined use has been found to be more informative than either marker alone.[28,29]

Serum IL-33 and sST2 offer complementary and potentially more sensitive biomarkers for monitoring cancer progression, response to therapy, and predicting prognosis, particularly when used alongside traditional markers. However, their utility as stand-alone diagnostic tools remain limited due to their associations with inflammatory diseases.[58,59] Further studies are needed to confirm their roles across.

8. IL-33 and ST2 as therapeutic targets

IL-33 plays a crucial role in maintaining tissue homeostasis, enhancing immune responses, and mediating fibrosis in chronic inflammation. It exerts its effects through its receptor ST2, found on various immune cells, including Tregs, ILC2s, myeloid cells, NK cells, Th1 and Th2 cells, and $CD8^+$ T cells. In cancer, IL-33 is downregulated in tumor cells but upregulated in the tumor stroma and serum. While IL-33 in tumor cells promotes type 1 antitumor immunity via $CD8^+$ T cells and NK cells, its presence in the tumor stroma and serum contributes to immune suppression through Tregs and MDSCs. Understanding IL-33's dual role in cancer offers potential for targeted immunotherapy.[60,61]

Given its dual function, IL-33 can be harnessed as a therapeutic target in cancer. The strategy involves manipulating the IL-33/ST2 signaling axis to enhance immune responses and shift the TME towards an anti-tumor state.

- By promoting IL-33 expression in tumor cells or selectively activating IL-33/ST2 signaling, it may help increase immune cell recruitment and activation, especially $CD8^+$ T cells and NK cells. This can improve immune surveillance and eliminate cancer cells more efficiently. IL-33 is involved in immune surveillance and cancer immunotherapy, where tumor development can trigger antitumor immune responses.
- Targeting IL-33 to reduce its pro-tumor effects in the tumor stroma could prevent immune suppression mediated by Tregs and MDSCs. This would reprogram the TME from one that suppresses immune responses to one that supports the activation of anti-tumor immunity.
- Immune checkpoint inhibitors (ICIs), such as anti-PD-1, anti-PD-L1, and anti-CTLA-4, have shown promise in cancer treatment by blocking the inhibitory signals that prevent T cells from attacking tumors. However, many tumors develop resistance to ICIs, often due to an immunosuppressive TME. IL-33 could synergize with ICIs. IL-33 could enhance the effectiveness of ICIs by reducing the immunosuppressive Tregs and MDSCs within the TME. This would make immune checkpoint inhibitors more effective by ensuring a more robust immune response.[8,60,61]

The IL-33/ST2 axis holds promise as both a biomarker and therapeutic target in cancer research. Future studies should focus on understanding how IL-33 modulates the immune response in specific cancer types. Robust clinical trials and multi-center studies are essential to validate the clinical utility of IL-33 and sST2, particularly for predicting treatment response and prognosis. Additionally, combining IL-33/ST2 targeting with other immunotherapies, such as checkpoint inhibitors, may enhance personalized treatment strategies. However, addressing the challenges of IL-33's dual role will require careful consideration of tumor-specific and immune-related factors.

The limitations of using serum IL-33 and sST2 in cancer research are multifaceted. The complexity of the IL-33/ST2 pathway presents a significant challenge, as it exhibits context-dependent biological roles that can vary across different tumor types and stages. Tumor heterogeneity further complicates the interpretation of serum IL-33 levels, making it difficult to establish a universal biomarker for all cancers. Additionally, variability in serum IL-33 levels, influenced by factors such as inflammation, chronic diseases, or infections, may confound results and reduce specificity. The lack of standardization in assays used to measure IL-33 and sST2 adds another layer of difficulty, as differences in sample

collection, storage, and assay techniques can lead to inconsistent findings. Moreover, the scarcity of longitudinal studies limits our understanding of how IL-33/ST2 function in cancer progression over time. Finally, despite promising preclinical findings, there is limited clinical validation, and the potential for non-specific effects further complicates the clinical application of serum IL-33 and sST2 in cancer diagnosis and treatment.

In conclusion, serum IL-33 and sST2 have proven to be valuable biomarkers in cancer research, offering crucial insights into tumor biology and immune response. Their potential lies in improving diagnostic accuracy, predicting prognosis, and personalizing treatment strategies for various cancers. Elevated IL-33 and sST2 levels are associated with tumor progression and immune evasion, highlighting their roles in the intricate relationship between the immune system and cancer. As ongoing research further uncovers their mechanisms, reliability, and clinical applications, IL-33 and sST2 could become integral to personalized cancer care, ultimately enhancing patient outcomes and informing treatment decisions. Continued exploration will be vital to fully harness their potential and optimize their clinical use. Additionally, the interaction between IL-33 and sST2 within the broader cytokine signaling network may offer promising therapeutic avenues for future cancer treatments.

Ethics approval and consent to participate

Not applicable.

Data availability statement

All data generated or analyzed during this study are included in this published article.

Authors' contributions

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All authors reviewed the results and approved the final version of the manuscript.

Patient's consent/Guardian's consent

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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