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Soluble Suppression of Tumorigenicity-2 as a Candidate Prognostic Marker for Stroke: A Systematic Review

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Background: Risk stratification of patients for incidence of stroke and its outcomes can aid in decision-making regarding treatment options and rehabilitative care. We systematically reviewed the literature to provide comprehensive evidence for the value of serum soluble suppression of tumorigenicity-2 (sST-2) in the prediction of stroke incidence and the evaluation of post-stroke outcomes.

Methods: The Medline, Scopus, Web of Science, and Embase databases were searched until the end of August 2022 for studies investigating the value of serum sST-2 in the prediction of stroke incidence and post-stroke outcomes.

Results: Nineteen articles were included. The articles reported conflicting results on the predictive value of sST-2 measurement in the incidence of stroke. Studies investigating the value of sST-2 measurement for the prognosis of post-stroke outcomes have reported positive associations between sST-2 levels and post-stroke mortality, composite adverse events, major disability, cerebral–cardiac syndrome, and cognitive impairment.

Conclusions: Although some studies have reported a predictive value of serum sST-2 measurement in the incidence of stroke, a clear consensus has yet to be reached because of discrepancies in the results. As for the prognosis of post-stroke outcomes, sST-2 may be a predictor of mortality, composite adverse events, and major disability after stroke. Overall, more well-designed prospective cohort studies are needed to reach a more decisive conclusion on the value of sST-2 measurement for the prediction of stroke and its outcomes and to determine optimal cutoffs.

Key Words: Soluble suppression of tumorigenicity-2, Stroke, Prognostic value

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INTRODUCTION

Stroke risk stratification is a valuable tool that healthcare providers can use to surveil and deliver timely preventive measures while increasing patients' awareness of potential stroke signs and symptoms. Determining the prognosis in the early stages after developing a stroke can contribute to acute and long-term medical management. Identifying patients who are at risk for unfavorable outcomes, such as death and long-term disability, in the first hours of admission can help physicians, patients, and their families make well-informed decisions regarding treatment options and rehabilitative care.

Conventionally, standardized neurological examination variables recommended by the National Institutes of Health Stroke Scale (NIHSS) are used for estimating stroke severity and outcomes [1]. Recently, the use of biomarkers as adjuncts for the

prediction of stroke and understanding the prognosis of post-stroke outcomes has increased. Among them, inflammatory biomarkers have been suggested as independent indicators of stroke severity and progression of secondary outcomes [2].

Suppression of tumorigenicity-2 (ST-2) is a member of the Toll-like/interleukin 1 (IL-1) receptor family that regulates inflammatory processes in many clinical conditions [3]. The ST-2 receptor family consists of two isoforms: transmembrane ST-2 and soluble ST-2 (sST-2). Upon binding of IL-33 with transmembrane ST-2, downstream signaling cascades possibly reduce inflammatory responses and subsequent apoptosis, fibrosis, and maladaptive tissue remodeling [4]. sST-2 is released into the systemic circulation and acts as a decoy receptor that suppresses the effect of IL-33 on target tissues [5]. sST-2 is broadly expressed in cardiac myocytes, epithelial cells, endothelial cells, smooth muscle fibers, and immune cells, making it a potential biomarker for inflammatory diseases (e.g., rheumatoid arthritis and asthma), cancers (e.g., breast and gastrointestinal cancers), and cardiovascular diseases, with most studies focusing on its role in heart failure [6, 7]. The Food and Drug Administration has approved sST-2 for the prediction of mortality in patients with chronic heart failure [8]. Intercorrelation between cardiac dysfunction and the risk of cerebrovascular accidents, shared common risk factors, and mutual post-injury molecular pathways have led to recent endeavors to explain the pathophysiological role of sST-2 in stroke. However, despite ample research, studies have reported conflicting results on the value of sST-2 in the prediction of stroke and its outcomes, and a clear consensus is lacking. Therefore, we systematically reviewed the current literature to provide comprehensive evidence for the value of serum sST-2 measurement in the prediction of stroke and the evaluation of post-stroke outcomes.

MATERIALS AND METHODS

Study design and search strategy

PICO was defined as: patients (P): patients at risk of stroke or patients with stroke, index test (I): serum sST-2 levels, comparison (C): patients not developing stroke or patients not developing the outcome of study after stroke, outcome (O): incidence of stroke or development of the outcome of study after stroke. Keywords were chosen according to MeSH and Emtree terms in the Medline and Embase databases, respectively, consultation with experts in the field, and review of related articles. We systematically searched the selected keywords in the Medline, Embase, Scopus, and Web of Science databases until August 30, 2022. A manual search was performed using the Google and Google Scholar search engines, and references in the related articles were studied to retrieve any possibly missed articles. The search strategies used are described in Supplemental Material 1.

Selection criteria

All human studies assessing the predictive value of serum sST-2 measurement in the incidence of stroke and its outcomes were included, regardless of sex, age, and race of the participants. Exclusion criteria for this study were duplicate studies, editorials and letters to the editor, not reporting stroke as an outcome, and reviews and articles not reporting the required data.

Data extraction

The titles and abstracts of the retrieved articles were independently evaluated by two reviewers. Next, the full texts of possibly related articles were reviewed in detail, and relevant articles were included in this study. The collected information was summarized into a checklist designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. Any disagreements were resolved with the help of a third reviewer. Information on study characteristics (first author name, publication year, and country), study type, included patient settings, sample size, mean age, number of male participants, follow-up period, type of stroke, studied outcome, number of patients with the outcome of study, time of serum sST-2 measurement, and sST-2 cutoff utilized were extracted. The predictive and prognostic values of serum sST-2 in the evaluation of stroke incidence and post-stroke outcomes were recorded as the effect size provided by each study, which included the odds ratio (OR), risk ratio (RR), and hazard ratio (HR) with related 95% confidence intervals (CIs).

Quality assessment and certainty of the findings

The quality of the articles was assessed using the QUADAS-2 guidelines for the assessment of diagnostic accuracy studies [10]. According to these guidelines, the risk of bias in articles is assessed in the domains of patient selection (sampling method and selection criteria), index test (blinding and pre-specification of a threshold/cutoff), reference standard (the reliability of the reference standard and blinding), and flow and timing (interval between test and reference standard, verification bias, and missing data). The QUADAS-2 guidelines also assess the applicability of the studies to the review question based on said domains.

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [11] was used to summarize

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the findings and assess the certainty of evidence. Any disagreements were resolved by consulting a third reviewer.

RESULTS

Study characteristics

The systematic search of online databases yielded 461 non-duplicate records, and 6 articles were acquired by a manual search. After evaluation, 19 articles were included in this systematic review [12-30] (Fig. 1), of which 10 investigated the value of serum sST-2 measurement in the prediction of the risk of stroke incidence [12-21], and the remaining 9 evaluated the value of serum sST-2 measurement in the prognosis of post-stroke outcomes [22-30]. A detailed description of the characteristics of these studies is provided in the respective sections.

Value of sST-2 measurement in the prediction of stroke

The included studies [12-21] comprised 24,160 patients, of whom 5.64% developed stroke. The follow-up period varied from 1 to 15 years. The characteristics and results of the studies evaluating the predictive value of serum sST-2 measurement in the incidence of stroke are provided in Table 1.

The studies reported conflicting results of the predictive value of serum sST-2 measurement in the incidence of stroke. In a study by Andersson, *et al.* [12], in a population without any past medical condition, serum sST-2 predicted both stroke/transient ischemic attack (TIA) and ischemic stroke incidence when the continuous serum value of sST-2 was included in the analyses (HR for stroke/TIA=1.6 and HR for ischemic stroke=1.77). However, the authors observed that only the third and fourth quartiles of serum sST-2 levels predicted the risk of stroke/TIA, whereas none of the sST-2 serum quartiles levels predicted ischemic stroke. Hammer, *et al.* [14] reported that in patients with diabetes undergoing hemodialysis, serum sST-2 levels >32.6 ng/mL predicted fatal stroke (HR=1.92), whereas sST-2 levels <32.6 ng/mL could not be used to predict the incidence of stroke. Polineni, *et al.* [19] reported that in patients undergoing coronary artery bypass graft/valve replacement surgery, serum levels of sST-2

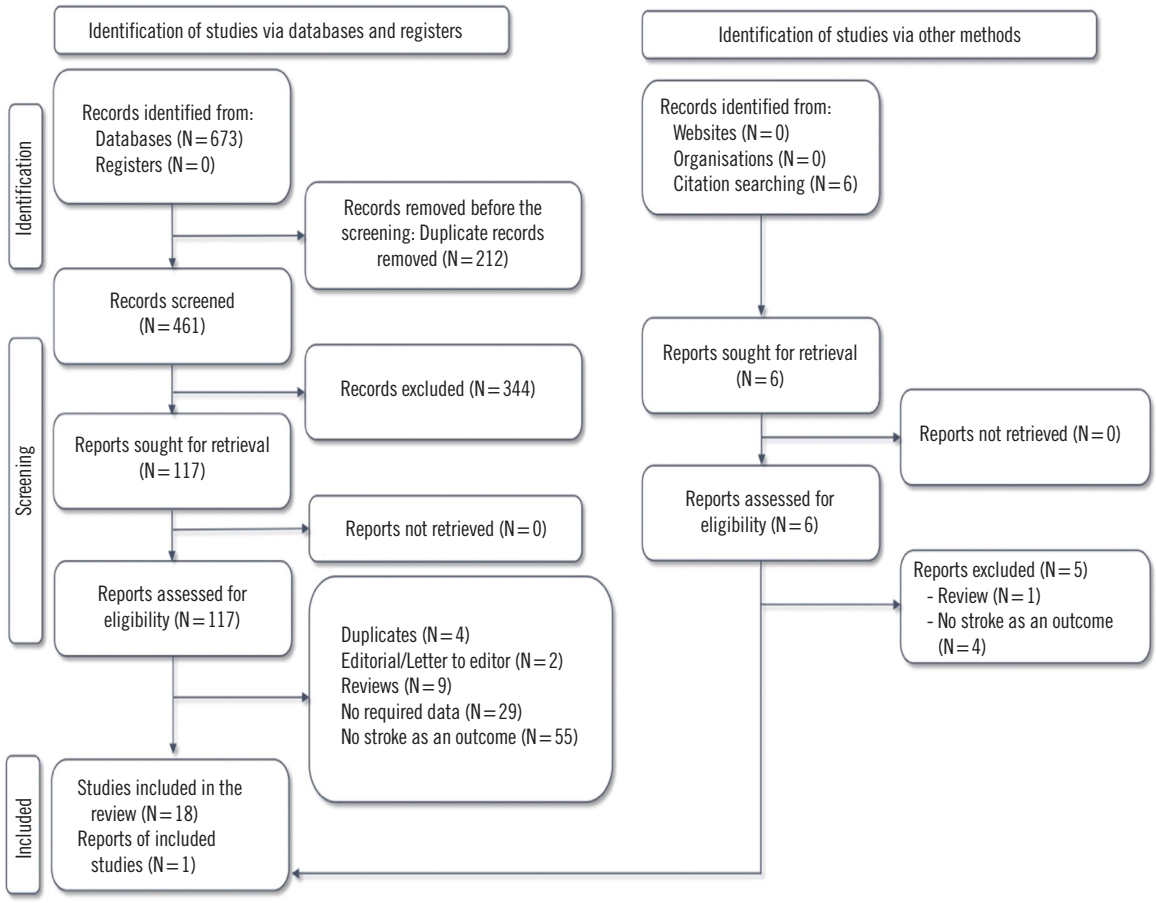

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of article selection.

Table 1. Summary of the included studies on the predictive value of sST-2 measurement in the incidence of stroke

Reference	Design	Patient setting	Sample size	Mean age, yr*	Number of male patients	Follow-up period	Outcome	N outcomes	sST-2 cutoff	Effect size (95% CI)
Andersson, 2015 [12]	PCS	Healthy subjects	2,741	59 ± 9.7	Not determined	11.8 ± 3 yr	Stroke/TIA	161	Q1 Q2 Q3 Q4 Continuous	*Ref.* HR = 1.42 (0.85–2.37) HR = 1.73 (1.05–2.84) HR = 1.76 (1.06–2.92) HR = 1.6 (1.01–2.54)
							Ischemic stroke	105	Q1 Q2 Q3 Q4 Continuous	*Ref.* HR = 1.47 (0.77–2.8) HR = 1.82 (0.97–3.41) HR = 1.85 (0.98–3.49) HR = 1.77 (1.01–3.12)
Bai, 2020 [13]	RCS	Hospitalized patients with CHD	1,113	65 (32–95)	NR	3.9 yr	Stroke	49	Trend over terciles	Effect size: NR $P < 0.001$
Hammer, 2022 [14]	PCS	Diabetic hemodialysis	1,196	66 ± 8.3	645	4 yr	Fatal stroke	94	Q1: < 20.1 ng/mL Q2: 20.1–25 Q3: 25.1–32.6 Q4: > 32.6	*Ref.* HR = 0.72 (0.39–1.33) HR = 1.51 (0.85–2.69) HR = 1.92 (1.17–3.14)
Hijazi, 2020 [15]	RCT	AF and at least one CHADS2 risk factor	4,406	70.1	2,789	1.9 yr	Ischemic stroke/ SEE	282	Third vs. first quartile	HR = 1.232 (1.05–1.446)
		AF and at least one of the following risk factors: previous stroke or TIA, CHF or reduced LVEF < 40%, age > 75 yr	1,218	72.2	612		Ischemic stroke/ SEE	149	Third vs. first quartile	HR = 1.02 (0.803–1.296)
Hughes, 2014 [16]	PCS	Healthy subjects	7,997	48.8 ± 22.1	4,225	15 yr	Stroke	354	Q1 Q2 Q3 Q4 Continuous	*Ref.* HR = 1.31 (0.91–1.89) HR = 1.15 (0.79–1.68) HR = 1.18 (0.82–1.71) HR = 1.03 (0.92–1.16)
Khamitova, 2019 [17]	PCS	Acute MI	180	61.4 ± 1.7	136	1.05 yr	Stroke	5	Above normal vs normal	Effect size: NR $P = 0.226$
Lidgard, 2022 [18]	PCS	Mild to moderate CKD	2,560	56 ± 11.6	1305	8.13 yr	Stroke	70	Q1: < 11 ng/mL Q2: 11–14.9 Q3: 14.9–20.1 Q4: > 20.1 Continuous	*Ref.* HR = 1.59 (0.75–3.36) HR = 1.21 0.56–2.63) HR = 1.43 (0.66–3.11) HR = 1.11 (0.86–1.44)
Polineni, 2018 [19]	PCS	CABG/valve replacement	1,554	65.3	1,188	NR	Stroke	NR	Median T1 T2 T3	OR = 3.34 (1.43–7.84) *Ref.* OR = 6.58 (1.48–29.32) OR = 7.58 (1.43–7.84)
Seo, 2019 [20]	PCS	Incident hemodialysis	182	61.3	106	1.7 yr	Non-fatal stroke	4	Median (59.5 ng/mL)	HR = 3.09 (0.32–29.7)
Somuncu, 2020 [21]	PCS	Acute MI	380	60.2	279	1 month 6 months 12 months	Stroke	3	35 ng/mL	Effect size: NR $P = 0.912$ $P = 0.052$ $P = 0.172$

*Age is reported as mean ± SD or median (range).
Abbreviations: PCS, prospective cohort study; RCT, randomized clinical trial; CHD, congestive heart disease; CHADS2, Congestive heart failure, Hypertension, Age ≥ 75 yrs, Diabetes, previous Stroke; AF, atrial fibrillation; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; MI, myocardial infarction; CKD, chronic kidney disease; CABG, coronary artery bypass graft; SEE, systemic embolic event; NR, not reported; HR, hazard ratio; OR, odds ratio; CI, confidence interval; T, tercile; Q, quartile; *Ref.,* reference.

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above the median of the study population predicted the risk of stroke (OR=3.34). Additionally, the authors observed that the second (OR=6.58) and third terciles (OR=7.58) of serum sST-2 levels could predict stroke.

Hijazi, *et al.* [15] studied the value of serum sST-2 levels for stroke prediction in two separate populations of patients with atrial fibrillation. The serum sST-2 level was shown to predict ischemic stroke/systemic embolic event only in one of the populations (HR=1.232). Bai, *et al.* [13] reported a significant relationship ($P<0.001$) between serum sST-2 levels and the prediction of stroke in patients with congestive heart disease.

The remaining studies, including Hughes, *et al.* [16] (patients without past medical condition), Seo, *et al.* [20] (patients on hemodialysis), Somuncu, *et al.* [21], Khamitova, *et al.* [17] (patients with acute myocardial infarction), and Lidgard, *et al.* [18] (patients with mild to moderate chronic kidney disease [CKD]), did not demonstrate a predictive value of serum sST-2 levels in the incidence of stroke.

Value of sST-2 measurement in the prognosis of post-stroke outcomes

The included studies [22-30] comprised 3,715 patients with stroke. The included patients had varying severities of stroke, and most populations had median stroke severity NIHSS scores between 2 and 6.

sST-2 levels were measured within 24 hours after administration. The follow-up period varied from in-hospital outcomes to outcomes after 1 year. Evaluated outcomes were mortality, composite adverse events, new stroke/mortality, modified Rankin Scale (mRS) of 3–6, post-stroke depression, cognitive impairment, hemorrhagic transformation, and cerebral–cardiac syndrome. The characteristics and results of the studies evaluating the value of sST-2 measurement in the prognosis of post-stroke outcomes are provided in Table 2.

Post-stroke mortality

Serum sST-2 levels at admission can predict mortality after ischemic stroke [22, 24, 28]. Dieplinger, *et al.* [22] and Wolcott, *et al.* [28] have reported that sST-2 predicted 3-month mortality with a RR of 3.77 and OR of 3.69, respectively. Mechtouff, *et al.* [24] reported an HR of 9.9 for 12-month mortality. The wide CI in this study was attributed to the low sample size and scarce event rate.

Unfavorable outcomes

Tian, *et al.* [26] reported that serum sST-2 levels could predict 1-year composite adverse events (death, myocardial infarction, ischemic and hemorrhagic stroke) and major disability (mRS 3–6)/death (HR for composite adverse events=2.517 and OR for major disability/death=3.126) in patients with TIA/ischemic stroke. Tian, *et al.* [27] also showed that serum sST-2 levels could predict mortality/new stroke in patients with TIA/ischemic stroke (HR=1.46). In a study of the prediction of unfavorable outcomes, Wolcott, *et al.* [28] reported that serum sST-2 levels could predict 3-month poor mRS (3–6) after ischemic stroke (OR=2.97).

Depression

Two studies on the value of sST-2 levels in the prediction of depression after stroke reported conflicting results. Lu, *et al.* [23] reported that serum sST-2 levels can predict depression severity after stroke (OR=1.2). However, Xu, *et al.* [29] did not observe this. It should be noted that in the study of Lu, *et al.* [23], only high sST-2 levels (>237.7 pg/mL) predicted depression severity after stroke.

Miscellaneous outcomes

Studies have demonstrated other possible uses of sST-2 measurement in the evaluation of stroke prognosis. Zhu, *et al.* [30] reported that sST-2 levels predicted cognitive impairment after stroke; Wolcott, *et al.* [28] reported that sST-2 predicted hemorrhagic transformation after stroke; and Sung, *et al.* [25] showed that sST-2 predicted mild and severe cerebral–cardiac syndrome. The study by Sung, *et al.* [25] had a low sample size, short follow-up period (in-hospital), and possibly a low event rate, which may have contributed to the wide CIs reported.

Risk of bias assessment

The quality of the articles was assessed using the QUADAS-2 guidelines. In the domain of patient selection, the risk of bias was rated as unclear in four studies as there was no mention of the sampling technique [17, 21, 22, 29]. In the domain of reference standard, three studies were rated as unclear in terms of risk of bias due to unclear stroke diagnosis criteria [17, 18, 21]. In the domain of flow and timing, one study was rated as unclear [19] because of not reporting follow-up, and one was rated as high [29] for a short-term follow-up period. The studies were rated as low in all other domains of the guidelines (Table 3).

Certainty of evidence

The certainty of the evidence was evaluated using the GRADE guidelines. As the included studies were considered observational studies, the base level of evidence was set as low. Certainty of ev-

Table 2. Summary of the included studies for the value of sST-2 measurement in prognosis of post-stroke outcomes

Reference	Design	Patient setting	Stroke severity*	Sample size	Mean age, yr	Number of male patients	Outcome	Follow-up period	N outcomes	sST-2 cutoff	Effect size (95% CI)
Dieplinger, 2015 [22]	PCS	Ischemic stroke	3 (3–7)	721	76 (66–84)	374	All-cause mortality	3 months	81	>32 ng/L	RR = 3.77 (2.33–6.57)
Lu, 2021 [23]	RCT	Acute ischemic stroke	4 (3–7)	635	60 ± 10.4	445	Post-stroke depression severity	3 months	250	Q1: < 117.5 pg/mL Q2: 117.5–162.8 Q3: 162.8–237.7 Q4: > 237.7 Continuous	*Ref.* OR = 1.07 (0.65–1.78) OR = 1.22 (0.73–2.02) OR = 1.84 (1.1–3.08) OR = 1.2 (1–1.43)
Mechtouff, 2021 [24]	PCS	Acute ischemic stroke	15 (10–19)	152	69 ± 15	90	All-cause mortality	12 months	12	Above median	HR = 9.9 (1.1–90.3)
Sung, 2020 [25]	PCS	Acute ischemic stroke	Mild (≤8), moderate (9–15), and severe (≥15)	99	64.4	59	Mild and severe cerebral–cardiac syndrome	In-hospital	NR	< 14,000 pg/mL ≥ 17,600 pg/mL	OR = 12.743 (3.836–42.328) OR = 23.448 (2.794–196.801)
Tian, 2019 [26]	PCS	TIA/ischemic stroke	2 (0–4)	413	60.3 ± 11.5	285	Composite adverse events (ischemic and hemorrhagic stroke, MI, all-cause death)	12 months	38	> 24.61 ng/mL	HR = 2.517 (1.279–4.956)
							Major disability (mRS 3–6) and death		40		OR = 3.126 (1.452–6.728)
Tian, 2020 [27]	PCS	TIA/ischemic stroke	2 (0–4)	430	60.2 ± 11.6	300	Mortality/new stroke	3 months	19	T1: < 11.85 ng/mL T2: 11.85–22.96 T3: > 22.96 Continuous	*Ref.* HR = 0.69 (0.11–4.12) HR = 5.14 (1.43–18.51) HR = 1.46 (1.15–1.87)
								12 months	38	T1: < 11.85 ng/mL T2: 11.85–22.96 T3: > 22.96 Continuous	*Ref.* HR = 1.31 (0.52–3.35) HR = 3 (1.29–6.97) HR = 1.27 (1.03–1.57)
Wolcott, 2017 [28]	PCS	Acute ischemic stroke	5 (2–12)	646	69 ± 15	346	Death mRS 3–6 Hemorrhagic transformation	3 months	29 84 36	NR	OR = 3.69 (1.54–9.32) OR = 2.97 (1.62–5.52) OR = 5.4 (1.4–35.61)
Xu, 2021 [29]	PCS	Acute ischemic stroke	Mild (1–4), moderate (4–15), and severe (>16)	160	50.8	69	Depression	In hospital (21 days)	60	NR	OR = 0.35 (0.18–0.69)
Zhu, 2021 [30]	RCT	Acute ischemic stroke	Median 4–6	619	60 ± 10.5	434	Cognitive impairment	3 months	325	Q1: < 117.6 pg/mL Q2: 117.60–163.51 Q3:163.51–238.77 Q4: ≥ 238.77	*Ref.* OR = 1.58 (0.97–2.56) OR = 1.65 (1.01–2.7) OR = 2.38 (1.42–4)

*Rated based on National Institutes of Health Stroke Scale (NIHSS) and reported as median (IQR).
Ages are presented as mean or mean ± standard deviation or median (IQR).
Abbreviations: PCS, prospective cohort study; RCT, randomized clinical trial; TIA, transient ischemic attack; MI, myocardial infarction; mRS, modified Rankin Scale; RR, relative risk; OR, odds ratio; HR, hazard ratio; NR, not reported; Q, quartile; T, tercile; *Ref.*, reference; IQR, interquartile range.

Table 3. Risk of bias assessment of the included studies

Reference	Risk of bias				Applicability			Overall
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard	
Studies on prediction of stroke								
Andersson, 2015 [12]	Low	Low	Low	Low	Low	Low	Low	Low
Bai, 2020 [13]	Low	Low	Low	Low	Low	Low	Low	Low
Hammer, 2022 [14]	Low	Low	Low	Low	Low	Low	Low	Low
Hijazi, 2020 [15]	Low	Low	Low	Low	Low	Low	Low	Low
Hughes, 2014 [16]	Low	Low	Low	Low	Low	Low	Low	Low
Khamitova, 2019 [17]	Unclear	Low	Unclear	Low	Low	Low	Low	Some concern
Lidgard, 2022 [18]	Low	Low	Unclear	Low	Low	Low	Low	Some concern
Polineni, 2018 [19]	Low	Low	Low	Unclear	Low	Low	Low	Some concern
Seo, 2018 [20]	Low	Low	Low	Low	Low	Low	Low	Low
Somuncu, 2020 [21]	Unclear	Low	Unclear	Low	Low	Low	Low	Some concern
Studies on prognosis of stroke								
Dieplinger, 2015 [22]	Unclear	Low	Low	Low	Low	Low	Low	Some concern
Lu, 2021 [23]	Low	Low	Low	Low	Low	Low	Low	Low
Mechtouff, 2021 [24]	Low	Low	Low	Low	Low	Low	Low	Low
Sung, 2020 [25]	Low	Low	Low	Low	Low	Low	Low	Low
Tian, 2019 [26]	Low	Low	Low	Low	Low	Low	Low	Low
Tian, 2020 [27]	Low	Low	Low	Low	Low	Low	Low	Low
Wolcott, 2017 [28]	Low	Low	Low	Low	Low	Low	Low	Low
Xu, 2021 [29]	Unclear	Low	Low	High	Low	Low	Low	Some concern
Zhu, 2021 [30]	Low	Low	Low	Low	Low	Low	Low	Low

Table 4. GRADE certainty of evidence and summary of findings

Outcome	Sample size Follow-up time	Risk of bias	Heterogeneity (I^2 value)	Indirectness	Imprecision	Publication bias	Quality of evidence*
Stroke	23,527 1–15 years	Not serious	Serious* (Q_1: *Ref.* Q_2: 0.00% Q_3: 0.00% Q_4: 80.76%)	Not serious	Not serious	Not present	Low ⊕⊕◯◯ Rated down one score • Possible heterogeneity Rated up one score • Possible dose-response gradient
Post-stroke mortality	1,519 3–12 months	Not serious	Not serious (0.00%)	Not serious	Serious	Not present	Moderate ⊕⊕⊕◯ Rated down one score • Imprecision (wide CIs) Rated up two scores • Possible dose-response gradient • Large effect size (>2)

Abbreviations: CI, confidence interval; *Ref.*, reference.
*The quality of evidence is presented as very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯), and high (⊕⊕⊕⊕) level of evidence.

idence was evaluated for outcomes of stroke and post-stroke mortality; the remaining outcomes were not assessed by a sufficient number of studies and thus were rated as having a very low level of evidence.

The studies on the value of sST-2 levels in the prediction of stroke were found to be heterogenous (I^2 up to 80.76% across quartiles; Supplemental Data Fig. S1). The level of evidence for the outcome of stroke was rated down one score due to heterogeneity and rated up one score due to the possible observed dose-response gradient, and therefore, the level of evidence for the outcome of stroke was rated as low. The level of evidence for the outcome of post-stroke mortality was rated down one score due to imprecision (wide CIs) and rated up two scores due to the possible observed dose-response gradient and large effect size (>2). No heterogeneity was observed in the studies on the outcome of post-stroke mortality (I^2: 0.00%; Supplemental Data Fig. S2). The level of evidence for the outcome of post-stroke mortality was rated as moderate (Table 4).

DISCUSSION

Acute risk stratification of patients for incident stroke and post-stroke prognostication could help tailor individual surveillance programs, rehabilitation, and preventive interventions. In addition to detailed neurological examination and imaging, serum biomarkers are objective and cost-effective tools that may aid physicians in diagnosing stroke. Furthermore, evaluating the role of biomarkers in post-stroke outcome prognoses can highlight different pathophysiological aspects of stroke and contribute to the development of novel targeted therapies.

Studies have reported conflicting results on the predictive value of serum sST-2 levels for the incidence of stroke. Two included studies [12, 16] were conducted in healthy subjects, and neither demonstrated a significant association between sST-2 levels and stroke. The inability of serum sST-2 levels to predict stroke in healthy subjects could be partly justifiable as the IL-33–ST-2 axis is involved in acute or chronic local and systemic inflammation, which may not be the case in healthy patients.

The studies investigating patients with preexisting cardiovascular comorbidities demonstrated that sST-2 could predict stroke in hospitalized patients with congestive heart disease [13] and patients undergoing coronary artery bypass graft or valve replacement surgery [19], but not in patients with incident myocardial infarction [17, 21]. The study conducted in two atrial fibrillation patient populations yielded conflicting results [15]. Overall, there is a significant body of evidence on the prognostic role of sST-2 levels in patients with cardiovascular disease. sST-2 is an independent predictor of rehospitalization due to heart failure, cardiovascular death, and all-cause mortality in patients with acute or chronic heart failure [7]. Concordantly, the American College of Cardiology and the American Heart Association have recommended sST-2 as an auxiliary tool for the prognosis of heart failure [31]. sST-2 can also predict outcomes in patients with coronary artery disease. A meta-analysis of patients with coronary artery disease demonstrated that increased sST-2 levels predicted an increased risk of major adverse cardiac events, heart failure, cardiovascular death, and all-cause mortality; however, sST-2 levels were not shown to predict myocardial infarction [32].

CKD and dialysis are major risk factors for atherosclerosis, cardiac dysfunction, and cardiovascular mortality [20, 33]. Two of the three included studies selectively conducted in patients with CKD reported the sST-2 level as an independent predictor of fatal stroke in patients on hemodialysis. Experimental studies have demonstrated that higher sST-2 levels are implicated in atherosclerotic plaque progression and instability, leading to coronary and cerebrovascular ischemic events, which is a culprit of higher morbidity and mortality in patients with CKD [18]. Brain natriuretic peptide and galectin-3 have been established as prognostic biomarkers in patients with renal dysfunction [18]. Compared to the mentioned biomarkers, the sST-2 level is less influenced by kidney function, making its interpretation in kidney impairment more reliable [14, 20]. Nevertheless, based on available studies, it would be premature to draw a conclusion about the predictive value of sST-2 for stroke incidence, and more studies are required.

The results of the included studies on the prognostic value of serum sST-2 for post-stroke outcomes showed fewer discrepancies than those of studies on the predictive value for stroke. Serum sST-2 levels have been associated with mortality and poor functional outcomes after stroke. Moreover, sST-2 is an independent predictor of post-stroke cerebral–cardiac syndrome, which highlights the role of sST-2 in cardiac dysfunction [25]. However, the prognostic value of sST-2 is not limited to the brain–heart axis.

There is convincing evidence that neuroinflammation plays a critical role in post-stroke secondary injuries and worsens outcomes after stroke [3, 34]. In the brain, IL-33 is constitutively expressed by astrocytes and oligodendrocytes and is released in large quantities immediately after injury [35]. Interaction between IL-33 and transmembrane ST-2 drives neuroinflammation toward the T helper type 2 and regulatory T cells with a subsequent release of anti-inflammatory cytokines, resulting in a repairing immune phase [36]. Animal models with knockout of the ST-2–IL-33 axis had a larger infarct size and higher mortality following brain injury [37]. External administration of IL-33 ameliorated the extent of experimental brain injury [38]. However, the sST-2 released after stroke competitively binds with IL-33 and blocks

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the interaction of IL-33 with its membrane receptor, hampering its neuroprotective effects. Studies have established a strong link between neuroinflammation and blood–brain barrier integrity [39]. In our study, sST-2 was demonstrated to contribute to the risk of hemorrhagic transformation in ischemic stroke. Accurate identification of patients at risk of hemorrhagic transformation is of great value as it would be informative for opting for eligible patients who would benefit from thrombolytic therapy. A recent systematic review and meta-analysis showed that matrix metalloproteinase-9 levels have the highest accuracy for detecting all subtypes of hemorrhagic transformation. The authors found only one study consistent with our results on the relevance of sST-2 levels in hemorrhagic transformation and emphasized the need for future research on this biomarker and its role in hemorrhagic transformation [34].

The included studies evaluating the role of sST-2 in the prediction of post-stroke depression [23, 29] and cognitive impairment [30] reported inconclusive results. Although the studies measured depression symptoms based on the Hamilton Rating Scale for Depression, the assessment time and proposed diagnostic cutoffs varied among the studies. Furthermore, enrolled patients had not been assessed for background depressive symptoms before the stroke incident. Altogether, there is a lack of sufficient evidence on the role of serum sST-2 levels in the prediction of psychological and cognitive impairments after stroke, and further studies with robust methodology are warranted.

We acknowledge that there are some limitations to our review, and caution should be applied when interpreting our results. First, we conducted a systematic review, but no meta-analysis because of differences in study methodologies and reported results. The studies included in the analysis differed in their patient setting and cutoffs used, with most studies not reporting the cutoffs used. The reported effect size also varied among the studies. We suggest that future studies report their findings in a more uniform format, with a report of cutoffs. It is important to note that, as for many other biomarkers, the incremental predictive and prognostic value of sST-2 levels should be assessed after integration with other well-established classic risk factors, biomarkers, and instrumental indicators. The temporal profile of and changes in sST-2 levels during patient follow-up should also be investigated, as patients with persistently high levels of sST-2 reportedly have higher mortality than patients with a decrease in sST-2 levels [40]. It is reasonable to expect that bulk release measurement, peak concentrations, or fluctuations in sST-2 levels after stroke can provide additional prognostic information. We did not evaluate other biomarkers reflecting inflammatory reactions and tissue remodeling. It would be reasonable to expect that adjustment for their values alters the predictive and prognostic value of sST-2. It should also be noted that there was a noticeable variation in assay methods, limits of detection, and the commercial kits used for sST-2 measurement among the studies. Additionally, some studies analyzed sST-2 levels in thawed samples that had been stored for many years, which may have affected biomarker stability.

In conclusion, our review demonstrated that although some studies have reported a predictive value of serum sST-2 levels in the incidence of stroke, no consensus can be reached because of discrepancies in the reported results. Studies on the value of serum sST-2 levels for the prognosis of post-stroke outcomes have shown that sST-2 can predict mortality, composite adverse events, and major disability after stroke. Overall, more well-designed prospective cohort studies are needed to reach a more decisive conclusion on the value of sST-2 levels for the prediction of stroke and its outcomes and to determine optimal cutoffs.

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AUTHOR CONTRIBUTIONS

Study design: Yousefifard M; data gathering: Ahmadzadeh K, Balabandian M, Yousefifard M; interpretation of the results: all authors; manuscript drafting and revision: all authors.

CONFLICTS OF INTEREST

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