

Systematic Review in Immunology and COVID-19

Serum-soluble ST2 as a novel biomarker for COVID-19 severity and mortality: A systematic review and meta-analysis

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Abstract

Introduction: While numerous biomarkers have demonstrated a link with the prognosis in patients with COVID-19, their practical applicability is constrained due to deficiencies in specificity, inadequate sensitivity, or a limited dynamic response. The objective of this systematic review and meta-analysis was to evaluate the role of the circulating soluble ST2 (sST2) levels as a predictive marker for the severity and mortality associated with COVID-19.

Methods: A systematic search was conducted in PubMed/MEDLINE, EMBASE, SCOPUS, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases until October 11, 2023 using well-defined search strategy. The occurrence of binary outcomes was determined through the computation of odds ratios (OR) with a 95% confidence interval (CI), employing the Mantel-Haenszel method. For continuous outcomes, the standard mean difference (SMD), along with a 95% CI, was the chosen metric. Pooled analysis was conducted using Stata version 17 (Stata Corp) and Review Manager v. 5.4 software (RevMan). The level of statistical significance was set at $p < 0.05$.

Results: Nine studies, including 1732 patients, met the eligibility criteria. A pooled analysis across trials indicates that sST2 levels are remarkably elevated in COVID-19 patients compared to non-COVID-19 individuals (39.3 ± 44.23 vs. 6.74 ± 6.25 ; SMD= 3.52; 95%CI: 1.72 to 5.32), significantly higher in severe than non-severe cases (94.07 ± 74.71 vs. 25.53 ± 7.36 ; SMD=3.87; 95%CI: 2.69 to 5.05), and vary between survivors and non-survivors (43.18 ± 21.54 vs. 119.11 ± 113.98 ; SMD= -2.84; 95%CI: -4.49 to -1.19), with substantial differences in means and confidence intervals reported across these groups ($p < 0.001$).

Discussion: The evidence presented herein highlights sST2 as a promising biomarker for the assessment of COVID-19 severity and prognosis. Its correlation with mortality and severe disease phenotypes positions it as a potential target for therapeutic modulation and a candidate for inclusion in prognostic models.

Take-home message: The meta-analysis identifies serum-soluble ST2 as a significant biomarker for assessing the severity and predicting mortality in COVID-19 patients, demonstrating its potential for guiding clinical decisions and treatment strategies.

Keywords: SARS-CoV-2; COVID-19; biomarker; prediction; sST2; Soluble ST2.

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INTRODUCTION

The COVID-19 pandemic has cast an enduring shadow over the world. The emergence of the COVID-19 pandemic caused by the SARS-CoV-2 virus has resulted in an unprecedented global health crisis, presenting an urgent need for effective strategies to manage and mitigate its impact on individuals and healthcare systems worldwide [1 – 3]. As we grapple with the ongoing pandemic, one of the critical questions that demands answers is our capacity to predict the trajectory and severity of COVID-19 [4]. Since the pandemic's emergence, there has been an urgent requirement to discover reliable diagnostic and predictive methods that can assist healthcare professionals in quickly evaluating the severity of the illness and forecasting its progression [5–7].

As we try to understand how this complicated illness develops and what might happen, biomarkers can help us a lot by providing important information. Biomarkers are molecular or biochemical indicators that reflect underlying physiological or pathological processes within the body [8]. These markers provide valuable insights into disease mechanisms, progression, and responses to therapeutic interventions [9]. In our effort to understand how biomarkers can predict COVID-19, it's important to know that scientists and doctors from around the world are working collaboratively across borders to investigate this issue [10,11].

In the context of COVID-19, several diagnostic methods, e.g., biomarkers, are routinely employed to assess the severity of COVID-19, among others high-sensitivity C-reactive protein, D-dimers, procalcitonin, ferritin, lymphocyte and haemoglobin count, interleukins, lactate dehydrogenase, aminotransferases, blood creatinine, creatine kinase, erythrocyte sedimentation rate, blood urea nitrogen, and platelet count [5,7,12–17]. These molecular signposts not only aid in diagnosis and prognosis but also hold the potential to guide therapeutic interventions [18–20]. Additionally, a wide range of lesser-known markers, particularly those with relevance in cardiology, have been explored in the context of COVID-19 [21,22]. These emerging bio-markers may offer valuable insights into the intricate cardiovascular implications of the disease.

Cardiac biomarkers, such as soluble interleukin 33 receptor (ST2), high-sensitivity troponin I (hs-TnI), vascular cell adhesion molecule-1 (VCAM-1), endothelial activation and stress index (EASIX) have garnered attention in the context of COVID-19 [21–23]. Hs-TnI, a sensitive indicator of cardiac injury, may signal myocardial stress among severe COVID-19 cases [21,22]. VCAM-1 reflects immune response and inflammation and is being studied for its potential role in assessing disease severity [21]. EASIX is emerging as a biomarker of endothelial activation and stress, shedding light on the vascular implications of COVID-19 [23]. However, in this publication, all the attention will be devoted to ST2, which resides on cell surfaces, manages immune responses, and navigates inflammatory processes [24]. While it has gained recognition for its significant involvement in various cardiovascular conditions [25], its prospective utility as a predictive biomarker within the framework of COVID-19 has increasingly captured the focus of rigorous research efforts [21–34]. Furthermore, combining the ST2 biomarker with other imaging studies, such as the Lung Ultrasound Zaragoza score (LUZ-score) provides a rapid and effective means of assessing the severity of COVID-19 [35]. The LUZ-score specialized lung ultrasound examination that allows for quick and efficient evaluation of lung involvement in the disease [33,35]. ST2 potential utility as a predictive biomarker in the realm of viral infections, particularly COVID-19, remains a subject of our research.

Understanding the prognostic significance of ST2 in COVID-19 has substantial implications for both clinical practice and research. Our analysis will provide an evidence of ST2's potential as a predictive biomarker. By summarizing our results with prior studies, we aspire to discern whether ST2's predictive prowess remains consistent across diverse populations, clinical settings, and methodological approaches. If ST2 levels prove to be indicative of disease severity and outcomes, clinicians could potentially use this biomarker to stratify patients based on risk, enabling more tailored treatment plans and efficient resource allocation. Additionally, these findings will expand our understanding of the complex immunological and inflammatory responses elicited by SARS-CoV-2 infection. In this backdrop, this systematic review and meta-analysis aim to evaluate soluble ST2 as a biomarker for the prognosis of COVID-19 severity and mortality.

METHODS

This systematic review and meta-analysis was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database under registration number CRD42023480208 and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards [37].

Search strategy

Source electronic databases: PubMed/MEDLINE, EMBASE, SCOPUS, and the Cochrane Central Register of Controlled Trials (CENTRAL).

Time frame: The search included all articles published in English up to October 11, 2023, across all databases, with no time restrictions. For each dataset, studies were identified using specific keywords.

Study types: The original articles published in peer-reviewed academic journals were included

Search strategy: Specific keywords. such as "SARS-CoV-2" OR "COVID-19" OR "novel coronavirus" OR "severe acute respiratory syndrome coronavirus 2" OR "nCOV" and "suppressor tumorigenicity biomarker 2" OR "ST2". In addition, the reference lists of the selected articles were manually screened for potentially relevant studies that could have been missed in the electronic databases.

Eligibility criteria

All research papers involving adult patients diagnosed with COVID-19 that provided data on ST2 levels along with clinical categorization or outcomes defined by validated clinical criteria for mortality or severity of COVID-19 were included in our study. We excluded certain types of publications: those not written in English, duplicates, and articles that were not original research (such as editorials, commentaries, letters to editors, review articles, case reports, or series).

Data extraction and risk of bias assessment

Two authors independently (K.D. and M.P.) extracted data from the studies, utilizing a specifically designed Excel spreadsheet for this task. To address any discrepancies between their findings, all authors collaborated to reach a unified decision. The data compiled encompassed various details: names of authors, country of origin, publication year, design of the study, size of the sample, average age, percentage of male participants, body mass index (BMI), and levels of suppressor tumorigenicity biomarker 2.

Two researchers (K.D. and F.C.) independently assessed the methodological integrity and potential for bias in qualifying studies. They employed the Newcastle-Ottawa Scale (NOS) for appraising the quality of these studies. This scale operates on a nine-point system, categorizing the

assessment into three domains: participant selection, comparability, and outcome determination [38]. The scoring system for the NOS in cross-sectional and case-control studies ranges from zero to a maximum of nine points. Studies that achieved a score of 7 or above on the NOS were deemed to be of high quality. In instances of disagreement regarding the NOS scoring, a third researcher (L.S.) was brought in to mediate and resolve these differences.

Statistical analysis

The studies were pooled using Stata version 17 (Stata Corp., College Station, Texas, USA) and Review Manager 5.4 (Cochrane Collaboration in Copenhagen, Denmark). A comprehensive synthesis of data was undertaken when at least two studies in the review provided information regarding the outcomes being examined. The occurrence of binary outcomes was determined through the computation of odds ratios (OR) with a 95% confidence interval (CI), employing the Mantel-Haenszel method. For continuous outcomes, the standard mean difference (SMD), along with a 95% CI, was the chosen metric. In cases where only the median was available, the approach outlined by Hozo and colleagues was applied to estimate the average [39]. The standard mean difference was also the basis for a traditional pairwise meta-analysis. The presence of heterogeneity among studies was assessed using Cochran's Q statistic, calculated with H and I² indices. The I² statistic was specifically used to quantify the proportion of variation attributable to heterogeneity across studies. Generally, I² values are interpreted as follows: 0–25% suggests low heterogeneity, 26–75% indicates a moderate level, and 76–100% points to a high degree of heterogeneity [40].

All analyses used random effects models by default, even when there was a lot of variation. This was because there was evidence that these models were more reliable in terms of outcomes than fixed effects models [41]. The examination of publication bias involved the use of a funnel plot, supplemented by Egger's correlation and Begg's regression tests for more objective analysis. However, assessing publication bias in other aggregated findings was not feasible due to the limited number of studies; a minimum of 10 studies is needed for such an assessment [42]. Statistical testing was based on two-tailed p-values, with the threshold for significance set at 0.05. Furthermore, a sensitivity analysis, excluding one study at a time, was conducted to evaluate the influence of individual studies on the overall aggregated result.

RESULTS

Study characteristics

An initial retrieval yielded 275 unique records. Once the duplicate entries were removed and five more records found through manual reference searching were added, the titles, abstracts, and full texts of these studies were looked at to see if they were relevant. This process culminated in the identification of 21 potentially pertinent publications. From this subset, 12 studies were subsequently excluded following a more detailed evaluation (Figure 1). Ultimately, a total of nine studies, including 1732 patients, met the eligibility criteria and were incorporated into the systematic review and meta-analysis [21,26–30,33,34,43].

Table 1 shows the characteristics and risk of bias assessment of the included studies, respectively. Studies originated in Italy, the USA, Spain, Norway, the Republic of Korea, Germany, and China. Table 1 also shows the baseline characteristics of the patient populations of the studies included in the meta-analysis.

Figure 1. Flowchart detailing selection and screening of the studies included in this review.

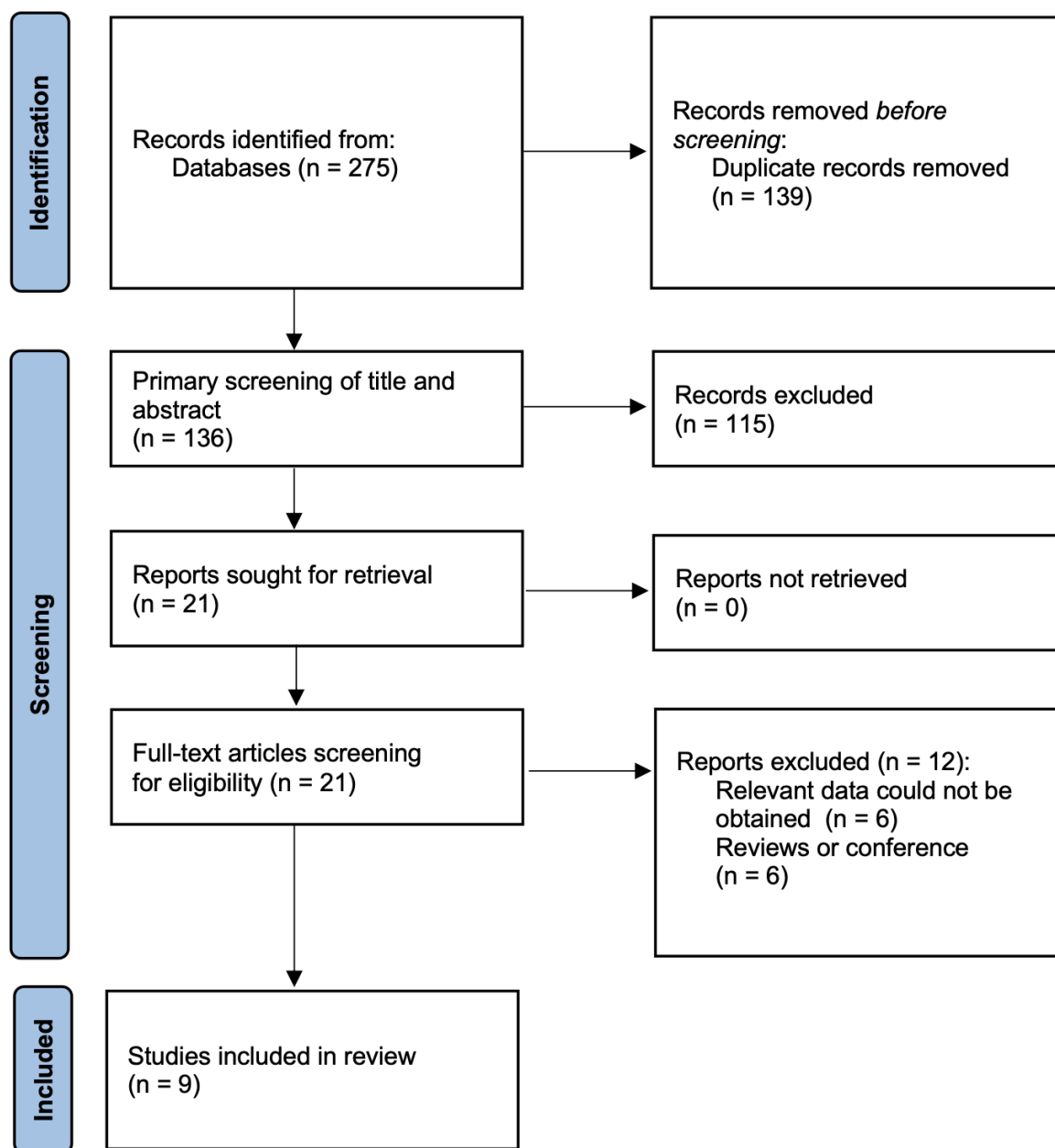


Table 1. Baseline characteristics of included trials (N=9 studies)

Study	Country	Study design	Study group	No.	Age, years	Sex, male	NOS score
Alladina et al., 2021	USA	Retrospective study	Severe	72	60.3 ± 12.7	45	8
			Non-severe	77	61.0 ± 16.3	50	
			Survived	42	57.1 ± 12.8	25	
			Decreased	30	64.6 ± 11.2	20	
	Spain		Severe	46	NS	NS	8

Arnaldos-Carrillo et al., 2023		Prospective observational study	Non-severe	449	NS	NS	
			Survived	450	55.9 [44.1, 69]	234 (52.1)	
			Decreased	45	77.0 [64, 82.0]	28 (62.2)	
Cabrera-Garcia et al., 2022	USA	Prospective cohort study	COVID-19	63	NS	NS	
			Non-COVID-19	43	NS	NS	8
			Severe	47	61	28 (59.6%)	
			Non-severe	16	59	8 (50.0%)	
Motloch et al., 2022	Italy	Prospective study	Survived	269	59 (49; 66)	108 (41.9%)	8
			Decreased	11	73 (61; 82)	6 (55.0%)	
Omland et al., 2021	Norway	Prospective study	Severe	35	NS	NS	
			Non-severe	88	NS	NS	7
			Survived	115	NS	NS	
			Decreased	8	NS	NS	
Park et al., 2023	Republic of Korea	Retrospective study	Severe	14	NS	NS	
			Non-severe	38	NS	NS	7
			Survived	40	NS	NS	
			Decreased	12	NS	NS	
Sabbatinelli et al., 2023	Italy	Retrospective cohort study	Survived	141	85(82–89)	48 (34.0%)	8
			Decreased	50	90(85–93)	21 (42.0%)	
Wendt et al., 2021	Germany	Prospective study	Survived	177	74 (62–83)	94 (53.11%)	8
			Decreased	44	80.5 (74–86)	28 (63.64%)	
Zeng et al., 2020	China	Prospective study	COVID-19	77	69 (24–88)	48 (62.3%)	
			Non-COVID-19	38	52 (23–69)	20 (52.6%)	9
			Severe	41	62 (29–88)	28 (68.3%)	
			Non-severe	36	54 (22–86)	20 (55.6%)	

Note: DM = diabetes mellitus; NS = not specified;

Outcomes

Pooled analysis of two trials [26, 33] showed that sST2 levels were statistically significantly higher in COVID-19 compared to non-COVID-19 patients and were 39.3 ± 44.23 and 6.74 ± 6.25 , respectively (SMD = 3.52; 95%CI: 1/72 to 5.32; $p < 0.001$). Six studies reported sST2 levels among severe vs. non-severe COVID-19 patients. Pooled analysis showed that ST2 levels were statistically significantly higher in the severe group compared to the non-severe COVID-19 group and were 94.07 ± 74.71 vs. 25.53 ± 7.36 , respectively (SMD=3.87; 95%CI: 2.69 to 5.05; $p < 0.001$; Figure 2).

Pooled analysis of sST2 levels among COVID-19 patients who survived vs. decreased varied and amounted to 43.18 ± 21.54 and 119.11 ± 113.98 , respectively (SMD = -2.84; 95%CI: -4.49 to -1.19; $p < 0.001$; Figure 3).

Figure 2. Forest plot of sST2 levels among severe vs. non-severe COVID-19 patients. The center of each square represents the mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

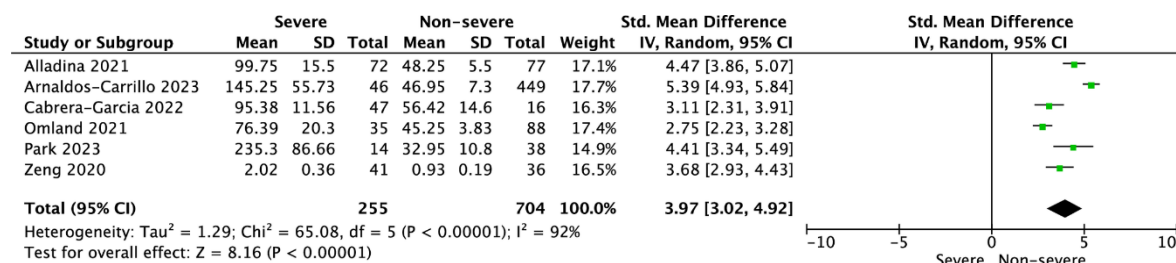
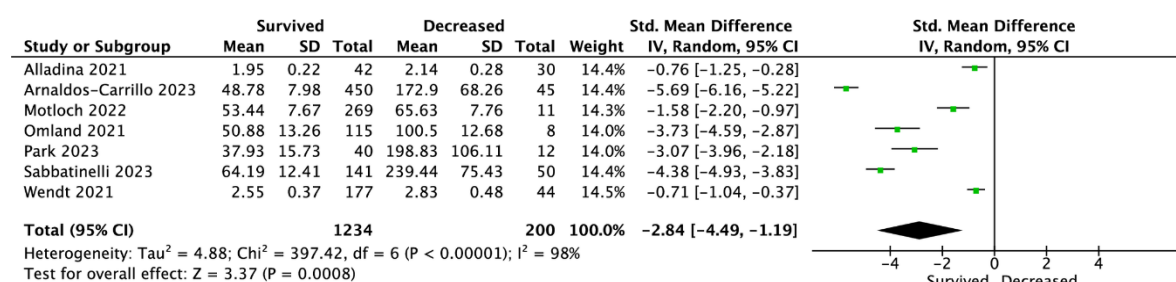


Figure 3. Forest plot of sST2 levels among survived vs. deceased COVID-19 patients. The center of each square represents the mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.



DISCUSSION

Our meta-analysis brings to the forefront the crucial role of ST2 as a biomarker in the clinical landscape of COVID-19. The elevation of serum ST2 levels in patients with COVID-19, particularly in severe cases and those resulting in mortality, sheds light on its potential involvement in the intricate pathophysiological pathways of the disease. This discussion aims to elaborate on these findings, contextualize them within the broader scope of current research, and address the clinical and prognostic implications of ST2 in the management of COVID-19.

The etiology of COVID-19 is characterized by a complex immunological response that begins with a phase of viral proliferation and culminates in an exacerbated inflammatory response for a portion of the affected population [44]. Such a cascade of inflammation is instrumental in the pathogenesis of acute respiratory distress syndrome (ARDS), multi-organ dysfunction, and, in extreme instances, mortality. It has been found that ST2, a member of the interleukin-1 receptor family, can show signs of systemic inflammation and myocardial strain. It splits into two types: a membrane-bound type called ST2L and a soluble type called sST2. The soluble type acts as a fake receptor for interleukin-33 (IL-33), which helps control the inflammatory environment.

This narrative of ST2's role in COVID-19, augmented by rigorous academic discourse and empirical substantiation, affords a deeper understanding of its implications in clinical settings. The ensuing paragraphs will delve into the nuanced interplay between ST2 and COVID-19 pathogenesis,

explicate the prognostic significance of ST2 levels, and examine the biomarker's potential to inform therapeutic strategies and clinical outcomes.

In the milieu of COVID-19, the pathophysiological significance of elevated soluble ST2 (sST2) levels has been posited to be an indicator of an amplified state of systemic inflammation. The mechanistic underpinnings of this hypothesis are anchored in the biological interactions of sST2 with its functional ligand, interleukin-33 (IL-33) [45]. IL-33 is a cytokine released consequent to cellular injury, acting as an alarmin that potentiates the immune system's responsivity. Scholarly investigations have elucidated that in the setting of COVID-19, where the immune response can become aberrantly hyperactive, the accrual of sST2 may represent a homeostatic countermeasure, endeavoring to mitigate this hyperactivity. The elevation of sST2 ostensibly functions by sequestering IL-33, thus curtailing its bioavailability for interaction with the membrane-bound ST2 ligand (ST2L) on immunocytes [25,26,46]. This sequestration ostensibly tempers the IL-33-mediated signaling cascades that would otherwise exacerbate the inflammatory response. Ergo, the heightened serum concentrations of sST2 observed in the severest COVID-19 contingents could be emblematic of a physiological attempt to attenuate the dysregulated immune dynamics characteristic of the disease's grave manifestations. This nuanced understanding of the sST2-IL-33 axis in the context of COVID-19 not only expands the biomolecular narrative of the disease but also augments the potential repertoire of biomarkers for gauging disease severity and therapeutic response.

The essence of a biomarker's prognostic utility is encapsulated in its capacity to forecast clinical endpoints, navigate therapeutic courses, and surveil the trajectory of a disease's progression. In line with this discussion, our meta-analysis results, along with supporting evidence from Omland et al. [34], show a strong link between sST2 levels and the range of disease severity and death in COVID-19 cohorts. This correlative potency of sST2, particularly in the context of intensive care unit (ICU) admissions and mortality rates, predicates its potential utility as a prognostic adjunct to be employed in concert with an array of clinical parameters. Such integration could efficaciously enhance the identification of patients predisposed to adverse outcomes. Using sST2 in this predictive framework could give clinicians the knowledge to ahead of time sort risk profiles, wisely distribute medical resources, and find the right level of patient monitoring, which would lead to better clinical management paradigms.

The fact that soluble ST2 (sST2) is linked to a number of inflammatory, coagulative, and cardiovascular markers not only gives us a better idea of how it plays a role in the development of COVID-19, but it also supports its potential as a multidimensional biomarker. The fact that severe COVID-19 symptoms are often accompanied by a heightened inflammatory response and coagulopathy, both of which are expected to make clinical outcomes worse, suggests that sST2 plays a key role in the underlying pathophysiological processes. Additionally, the fact that high sST2 levels are linked to signs of thromboembolic events and myocardial distress shows how useful it is for letting us know how bad the damage is to the whole body. This suggests that sST2 may be a sign of the thrombo-inflammatory effects that come with having a severe disease. This integrative biomarker profile of sST2 therefore emerges as a quintessential element in the paradigm of biomarker-guided management of COVID-19, furnishing clinicians with a tool that potentially transcends the capabilities of traditional single-axis markers.

The corroborative evidence substantiating the utility of soluble ST2 (sST2) as a biomarker beckons its judicious assimilation into clinical practice, warranting a deliberate and methodical approach. The incorporation of sST2 level determinations into the standard laboratory protocol for patients hospitalized with COVID-19 is proposed, with the caveat that such measurements should be meticulously interpreted. It is important to recognize that sST2 levels can be affected by other factors, especially cardiovascular diseases that were already present, which can make their true clinical significance harder to understand [47,48]. Also, it is vital to quickly and accurately find the sST2 thresholds that can be used in clinical settings, meaning that they can reliably tell the difference between the different levels of disease severity and predict the course of the disease in the COVID-19 setting [49,50]. These endeavors to refine the clinical applicability of sST2 will enhance its prognostic precision and cement its status as an integral component of patient assessment and management [51-54].

Our study, albeit insightful, is not without limitations. The pooled analysis, while robust, is derived from a limited number of studies and populations. Larger studies with diverse cohorts are essential to validating our findings. Additionally, the dynamic nature of sST2 levels during the course of the COVID-19 infection and the impact of therapeutic interventions on these levels warrant further investigation. Future research should aim to unravel the temporal changes in sST2 levels in relation to disease progression, therapeutic responses, and recovery. Longitudinal studies could show if the drop in sST2 levels is linked to better health, proving that it is a useful tool for tracking the progression of a disease. Moreover, mechanistic studies are needed to understand the role of the IL-33/ST2 axis in the immunopathology of COVID-19.

CONCLUSION

The evidence presented herein highlights sST2 as a promising biomarker for the assessment of COVID-19 severity and prognosis. Its correlation with mortality and severe disease phenotypes positions it as a potential target for therapeutic modulation and a candidate for inclusion in prognostic models.

Author Contributions: Conceptualization: KD, LS.; methodology: KD, and LS; software: MP, LS.; validation: LS, GN, SG, and KK; formal analysis, LS, KD, AK; investigation: KD, LS, MP, DS, AK and GN; resources: KD, LS; data curation: KD, LS, MP, DS, AK and GN; writing—original draft preparation: KD, LS, MP, DS, MT, and KK; writing—review and editing, all authors; visualization: KD, LS; supervision: LS; project administration: MM. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: None

Data Availability Statement: Some or all data and models that support the findings of this study are available from the corresponding author upon reasonable request.

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