Prognostic factors for streptococcal toxic shock syndrome: systematic review and meta-analysis

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ABSTRACT

Objectives To quantify the prognostic effects of demographic and modifiable factors in streptococcal toxic shock syndrome (STSS).

Design Systematic review and meta-analysis.

Data sources MEDLINE, EMBASE and CINAHL from inception to 19 September 2022, along with citations of included studies.

Eligibility criteria Pairs of reviewers independently screened potentially eligible studies of patients with Group A Streptococcus-induced STSS that quantified the association between at least one prognostic factor and outcome of interest.

Data extraction and synthesis We performed random-effects meta-analysis after duplicate data extraction and risk of bias assessments. We rated the certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluation approach.

Results One randomised trial and 40 observational studies were eligible (n=1918 patients). We found a statistically significant association between clindamycin treatment and mortality (n=144; OR 0.14, 95% CI 0.06 to 0.37), but the certainty of evidence was low. Within clindamycin-treated STSS patients, we found a statistically significant association between intravenous Ig treatment and mortality (n=188; OR 0.14, 95% CI 0.06 to 0.37), but the certainty of evidence was low. Within clindamycin-treated STSS patients, we found a statistically significant association between intravenous Ig treatment and mortality (n=188; OR 0.34, 95% CI 0.15 to 0.75), but the certainty of evidence was low. The odds of mortality may increase in patients ≥65 years when compared with patients 18–64 years (n=396; OR 2.37, 95% CI 1.47 to 3.84), but the certainty of evidence was low. We are uncertain whether non-steroidal anti-inflammatory drugs increase the odds of mortality (n=50; OR 4.14, 95% CI 1.13 to 15.14; very low certainty). Results failed to show a significant association between any other prognostic factor and outcome combination (very low to low certainty evidence) and no studies quantified the association between a prognostic factor and morbidity post-infection in STSS survivors.

Conclusions Treatment with clindamycin and within clindamycin-treated patients, IVIG, was each significantly associated with mortality, but the certainty of evidence was low. Future research should focus on morbidity post-infection in STSS survivors.

INTRODUCTION

Streptococcal toxic shock syndrome (STSS) is an acute and severe life-threatening complication of predominantly invasive Group A Streptococcus (GAS) infections. STSS is relatively uncommon, but is fatal.1 Using US data from 2000 to 2004, the Centers for Diseases Control and Prevention estimated an annual incidence rate of 0.2 cases per 100,000 people and a fatality rate of 36%.2 STSS has important consequences for morbidity as well, in which patients may require radical surgical debridement, and patients with organ failure may have permanent respiratory and renal insufficiency.1

Although extensive multidisciplinary clinical management efforts by intensivists, infectious disease specialists and surgeons have curbed STSS all-cause mortality,3 data on the natural history of long-term sequelae in surviving patients, such as renal, respiratory and neuropsychiatric complications, are sparse.1,4 Published studies of prognostic and treatment factors for STSS have consistently focused on associations with all-cause mortality,5,11 with few reporting on outcomes capturing the morbidity post-infection in STSS survivors.7,12 Furthermore, a thorough and systematic review to corroborate this evidence is lacking. A narrative review of
STSS was limited by the lack of a systematic or explicit search of the literature, it included studies that were only narratively synthesised, and the focus was limited to studies within a critical care setting.1

Understanding prognosis of STSS is important for patients, clinicians and healthcare decision makers. We conducted a systematic review to summarise the prognostic and treatment factors, and outcomes of STSS. We aimed to capture a wide breadth of patient-important outcomes with follow-up that included both short-term and long-term outcomes within and outside of critical care.

MATERIALS AND METHODS
We registered a protocol for the present systematic review and meta-analysis with PROSPERO (CRD42020166961).15 16 We report this systematic review and meta-analysis following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analyses of Observational Studies in Epidemiology checklists.17 18 Decisions regarding criteria for study inclusion, search methods for identification of studies, data collection, risk of bias, evaluation of the certainty of evidence and analysis were established a priori.

Search strategy and selection criteria
We searched MEDLINE (OVID interface, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, 1946–19 September 2022), EMBASE (OVID interface, 1974–19 September 2022) and the Cumulative Index to Nursing And Allied Health Literature (CINAHL) from inception to 19 September 2022, with no restrictions on publication date. We applied search filters for randomised controlled trials and non-randomised studies (cohort, case-control and case series with at least two STSS patients),19 20 and tailored search strategies to each database. We restricted included studies to the English language to facilitate screening of full texts21 22 and searched citations of included studies to minimise the risk of failing to include relevant studies.

We included studies of randomised and non-randomised designs that reported the association of at least one prognostic factor of interest with at least one outcome of interest, and compared GAS-induced STSS patients with the prognostic factor of interest (ie, exposed) to GAS-induced STSS patients without the prognostic factor of interest (ie, unexposed). Studies of patients with microbiologically confirmed STSS, probable cases of STSS and patients with clinical evidence of STSS as defined by study authors and generally consistent with the below criteria were eligible.23 Clinical evidence of STSS included hypertension and at least two of the following: renal impairment, coagulopathy, liver function abnormality, acute respiratory distress syndrome, generalised erythematous macular rash (with desquamation), soft-tissue necrosis (including necrotising fasciitis, myositis or gangrene) or meningitis. Probable cases of STSS were defined as meeting clinical evidence with GAS isolated from a non-sterile site (eg, throat, sputum, superficial skin lesion) or antigen detected. Confirmed cases of STSS were defined as meeting clinical evidence with GAS isolated from a sterile site (eg, blood, cerebrospinal fluid, deep tissue specimen taken during surgery).3 25 Demographic, comorbidity, infection, modifiable and process variables were prognostic factors of interest. Informed by clinical expertise in the review team, we selected outcomes based on importance to patients. Further, we aimed to capture the long-term sequelae in patients surviving STSS.1 12 14

We chose the following outcomes of interest: (time to) mortality, hospital length of stay, intensive care unit (ICU) admission, ICU length of stay, mechanical ventilation, duration of mechanical ventilation, (time to) clinical cure/improvement or resolution of shock, change in Sequential Organ Failure Assessment (SOFA) score from baseline, functional status (eg, physical component summary score on the 36-item Short Form Health Survey) and health-related quality of life (HRQoL). We also extracted cost outcomes, which are relevant to hospital and patient payees.

We excluded case reports and conference abstracts, and studies in which the population was less than 80% GAS-induced STSS cases (ie, toxic shock syndrome of bacterial aetiologies other than GAS made up more than 20% of the study population). Because prognostic evidence in STSS patients is scarce,1 12 14 we did not apply any restrictions based on analytical method (eg, conducting an adjusted, multivariable analysis) or sample size.

Using a systematic review software, Rayyan,24 following training and calibration exercises, pairs of reviewers independently screened all titles and abstracts, followed by full-texts of records that were identified as potentially eligible. When necessary, consensus was reached through discussion between the review pair, and arbitration by a senior coinvestigator in the absence of consensus.

Data analysis
For each eligible study, pairs of reviewers extracted data independently using a standardised, pilot-tested data extraction form. Reviewers collected information on study characteristics (study design as defined by study authors, sample size, country), patient characteristics (age, sex), disease characteristics (confirmed vs probable STSS, presence of necrotising fasciitis), prognostic factors and outcomes of interest (means or medians and measures of variability for continuous outcomes and the proportion of participants who experienced an event for dichotomous outcomes). If multiple time points were reported for outcomes of interest, we extracted all time points. To minimise risk of confounding associated with prognostic effect estimates on dichotomous outcomes in non-randomised studies, we preferentially extracted adjusted ORs and corresponding 95% CIs over proportions when both were reported. We used the proportions to calculate crude ORs when no adjusted ORs were provided.
Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a senior coinvestigator.

Following training and calibration exercises, reviewers, independently and in duplicate, used the Quality in Prognosis Studies (QUIPS) tool to rate each prognostic factor and outcome combination at low, moderate or high risk of bias. Based on prespecified sets of questions, we assessed risk of bias across the following domains: participation, attrition, prognostic factor measurement, outcome measurement, confounding and statistical analysis and reporting.\textsuperscript{25} For studies addressing more than one prognostic factor and outcome combination, we reported the highest risk of bias rating among the prognostic factor and outcome combinations within a study for each domain. In addition to assessing risk of bias at the domain level as outlined in the QUIPS tool, we applied the following rules to assess risk of bias overall at the study level. We rated overall study risk of bias as low if the study was prospective and five or more domains were assessed as low risk of bias, and high if two or more domains were assessed as high risk of bias. All other studies were rated as moderate risk of bias overall. Due to high risk of selection bias and residual confounding, we rated all case series as high risk of bias overall. Reviewer pairs resolved discrepancies by discussion and, when needed, with adjudication by a senior coinvestigator.

Pairs of reviewers used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to independently assess the certainty of prognostic evidence for each meta-analysed outcome. Criteria for rating the certainty for each prognostic factor and outcome as high, moderate, low or very low, included considerations of risk of bias, inconsistency, indirectness, size and precision of the association and publication bias.\textsuperscript{26,27} Judgements of imprecision for this systematic review were made using a minimally contextualised approach. This approach considers whether CIs include the null effect. Further, the terminology used to report GRADE ratings (eg, low certainty evidence) is based on published GRADE guidance.\textsuperscript{28,29} The online supplemental file presents the detailed guidance we developed to facilitate the certainty of the evidence assessment in this review. To facilitate interpretation of the results in which the summary measure was an OR, we used the median event rate in the reference group of studies reporting proportions to calculate baseline risks and subsequently calculated absolute effects. GRADE evidence summaries (Summary of Findings tables) were generated in the MAGIC Authoring and Publication Platform (www.magicapp.org).

When at least two included studies reported on the same prognostic factor and outcome in patients with GAS-induced STSS, we conducted DerSimonian and Laird random-effects meta-analyses using the metafor package in R V.4.0.4 (R Studio, Boston, Massachusetts, USA).\textsuperscript{30} We summarised the effects of prognostic factors on dichotomous outcomes using ORs and corresponding 95% CIs, and on continuous outcomes using mean differences and corresponding 95% CIs. For prognostic factor and dichotomous outcome combinations in which every patient in the reference arm experienced the outcome, we summarised the effects by directly calculating risk differences and corresponding 95% CIs. We set the criterion for statistical significance at alpha=0.05. Visual inspection of forest plots and the chi-square test were performed to evaluate heterogeneity. We interpreted an $I^2$ statistic value of 0%–40%, 30%–60%, 50%–90% or 75%–100% as not likely important, moderate, substantial or considerable heterogeneity, respectively.\textsuperscript{31} If an $I^2$ statistic value was within a range of overlapping values (eg, 80%), we would interpret heterogeneity as more important (eg, consider-able instead of substantial) if the meta-analysis contained few studies, we observed inconsistent magnitudes and directions of summary estimates on visual inspection of the forest plots, or the $\chi^2$ test was significant.\textsuperscript{31} For meta-analyses of continuous outcomes, we imputed means and SD for studies reporting medians and IQR, respectively.\textsuperscript{32,33}

Patient-level data from case series were aggregated when possible to enable comparative analysis via meta-analysis. We planned to perform a regression analysis for each study for which age was reported at the patient level to generate a study and age category (0–17 years old vs 18–64 years old vs 65 years old or older) specific OR that could be used in meta-analysis when a study had at least 10 observations for continuous outcomes and 10 events for dichotomous outcomes; however, no study met the sample size or event number requirements. Further, scarcity and variability of data precluded our plan to narratively synthesise the evidence from included studies for which meta-analysis of a prognostic factor and outcome combination was not possible.

The analysis plan included performing subgroup analyses of STSS patients treated with clindamycin versus no clindamycin, STSS patients with necrotising fasciitis versus without necrotising fasciitis, age (0–17 years old vs 18–64 years old vs 65 years old or older), sex (male vs female) and risk of bias (high vs moderate vs low) when at least two studies were present for each subgroup. Because select meta-analyses were limited by small numbers of events, we performed a post hoc sensitivity analysis using the Peto method for meta-analysis, which is recommended for meta-analysis of rare events,\textsuperscript{34} and compared the results to those from the DerSimonian and Laird method we applied in this review.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

After screening 27321 titles and abstracts, and 305 full texts, 41 studies that reported on the association between at least one prognostic factor and outcome of interest in
STSS patients proved eligible (figure 1). All but one study (40/41, 98%) were non-randomised. Eligible studies were published between 1989 and 2021, ranged in sample size from 2 to 476, included 1918 STSS patients in total and were conducted in 22 different countries, most commonly in the USA (15/41, 37%).

Table 1 describes the characteristics of included studies reporting on the association of at least one prognostic factor and outcome of interest. The online supplemental data includes additional study characteristics for each study. Of the 41 included studies, 29 (71%) reported on demographic prognostic factors of interest, 5 (12%) medical history of being immunocompromised, 11 (27%) early disease characteristics and 16 (39%) treatment. Of the dichotomous outcomes, mortality was most commonly reported (36/41, 88%), followed by ICU admission (10/41, 24%), clinical cure or improvement (6/41, 15%). Few studies reported on hospital (3/41, 7%) and ICU length of stay (2/41, 5%). Two studies reported on time to mortality in days; however, only one reported sufficient data precluding meta-analysis. 

The online supplemental file includes the forest plots depicting the studies included in the meta-analysis of each prognostic factor-outcome combination. It also includes the list of studies reporting on prognostic factor-outcome combinations of interest that were not eligible for any meta-analysis, along with the reasons for exclusion from meta-analysis.

Risk of bias in included studies

Online supplemental file presents the risk of bias assessment of the 41 included studies. The majority of studies were rated as high risk of bias overall owing to residual...
is true for patients ≥65 years compared with patients <18 years (n=136, OR 10.66, 95% CI 1.28 to 88.57; very low certainty of evidence). We are also uncertain whether non-steroidal anti-inflammatory drugs (NSAIDs) increase the odds of mortality (n=50, OR 4.14, 95% CI 1.13 to 15.14; very low certainty of evidence). Very low certainty evidence failed to show a significant association with any other prognostic factor and mortality in STSS patients: male versus female (n=80, OR 0.95, 95% CI 0.36 to 2.52), patients <18 years vs patients 18 to 64 years (n=694, OR 0.54, 95% CI 0.15 to 1.94), immunocompromised versus not immunocompromised (n=33, OR 1.65, 95% CI 0.33 to 8.26), necrotising fasciitis versus no necrotising fasciitis (n=840, OR 0.81, 95% CI 0.51 to 1.29), acute renal failure versus no acute renal failure (n=91, OR 2.50, 95% CI 0.97 to 6.42), haemodialysis versus no haemodialysis (n=42, OR 1.94, 95% CI 0.22 to 16.99) and any antibiotic versus no antibiotic (n=19, OR 0.48, 95% CI 0.05 to 4.76).

Prognostic factors for ICU admission
Six prognostic factors from eight studies including 174 patients were eligible for analysis (table 2, online supplemental data). We found no statistical evidence of an association between any prognostic factor and ICU admission: male versus female sex (n=19, OR 2.87, 95% CI 0.29 to 28.27), necrotising fasciitis versus no necrotising fasciitis (n=28, OR 0.74, 95% CI 0.12 to 4.48), haemodialysis versus no haemodialysis (n=13, OR 3.25, 95% CI 0.21 to 50.35), NSAIDs versus no NSAIDs (n=15, OR 0.86, 95% CI 0.06 to 12.48), IVIG treatment versus no IVIG treatment (n=156, OR 1.09, 95% CI 0.43 to 2.77) and antibiotic treatment versus no antibiotic treatment (n=14, OR 4.60, 95% CI 0.29 to 72.98). The certainty of all ICU admission evidence was very low due to very serious risk of bias and imprecision.

Prognostic factors for clinical cure or improvement
Four prognostic factors from six studies including 38 STSS patients were eligible for analysis (table 2, online supplemental data). We found no statistical evidence of an association between any prognostic factor and clinical cure or improvement: male versus female sex (n=23, OR 3.33, 95% CI 0.47 to 23.59), necrotising fasciitis versus no necrotising fasciitis (n=24, OR 0.34, 95% CI 0.02 to 5.20), haemodialysis versus no haemodialysis (n=26, OR 1.43, 95% CI 0.15 to 14.08) and IVIG treatment versus no IVIG treatment (n=23, OR 0.27, 95% CI 0.02 to 3.76). The certainty of all clinical cure or improvement evidence was very low due to very serious risk of bias and serious or very serious imprecision.

Prognostic factors for mechanical ventilation
Five prognostic factors from six studies including 170 STSS patients were eligible for analysis (table 2, online supplemental data). We found no statistical evidence of an association between any prognostic factor and need for mechanical ventilation: male versus female sex (n=21, OR 2.09, 95% CI 0.32 to 13.74), necrotising fasciitis...
Table 2  Summary of findings for prognostic factor—outcome meta-analyses

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>No of patients (studies)</th>
<th>OR (95% CI)</th>
<th>Absolute effect estimates</th>
<th>GRADE: certainty of the evidence</th>
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<tbody>
<tr>
<td><strong>Mortality</strong></td>
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<tr>
<td>Demographic</td>
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<tr>
<td>Male versus female</td>
<td>80 (13)</td>
<td>0.95 (0.36 to 2.52)</td>
<td>250 per 1000 241 per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision</td>
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<tr>
<td>&lt;18 vs 18–64 years</td>
<td>694 (5)</td>
<td>0.54 (0.15 to 1.94)</td>
<td>234 per 1000 142 per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision</td>
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<tr>
<td>≥65 vs &lt;18 years</td>
<td>136 (2)</td>
<td>10.66 (1.28 to 88.57)*</td>
<td>50 per 1000 359 per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision, and serious inconsistency</td>
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<tr>
<td>≥65 vs 18–64 years</td>
<td>396 (2)</td>
<td>2.37 (1.47 to 3.84)*</td>
<td>193 per 1000 362 per 1000</td>
<td>Low</td>
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<td>Due to very serious risk of bias</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Immunocompromised versus not Immunocompromised</td>
<td>33 (4)</td>
<td>1.65 (0.33 to 8.26)</td>
<td>438 per 1000 563 per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision</td>
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<tr>
<td>Early disease</td>
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<tr>
<td>Acute renal failure versus no acute renal failure</td>
<td>91 (4)</td>
<td>2.50 (0.97 to 6.42)</td>
<td>NA per 1000 NA per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision</td>
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<tr>
<td>Necrotising fasciitis versus no necrotising fasciitis</td>
<td>840 (10)</td>
<td>0.81 (0.51 to 1.29)</td>
<td>347 per 1000 301 per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision</td>
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<tr>
<td>Treatment</td>
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<tr>
<td>IVIG versus no IVIG (all STSS patients)</td>
<td>365 (9)</td>
<td>0.37 (0.17 to 0.80)*</td>
<td>231 per 1000 100 per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and serious imprecision</td>
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<tr>
<td>IVIG versus no IVIG (subset of STSS patients treated with clindamycin)</td>
<td>188 (6)</td>
<td>0.34 (0.15 to 0.75)*</td>
<td>300 per 1000 127 per 1000</td>
<td>Low</td>
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<td>Due to serious risk of bias and imprecision</td>
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<tr>
<td>Any antibiotic versus no antibiotic</td>
<td>19 (3)</td>
<td>0.48 (0.05 to 4.76)</td>
<td>NA per 1000 NA per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision</td>
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<tr>
<td>Clindamycin versus no clindamycin antibiotic</td>
<td>144 (4)</td>
<td>0.14 (0.06 to 0.37)*</td>
<td>800 per 1000 359 per 1000</td>
<td>Low</td>
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<tr>
<td>Haemodialysis versus no haemodialysis</td>
<td>42 (4)</td>
<td>1.94 (0.22 to 16.99)</td>
<td>107 per 1000 189 per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision</td>
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<tr>
<td>NSAIDs vs no NSAIDs</td>
<td>50 (4)</td>
<td>4.14 (1.13 to 15.14)*</td>
<td>100 per 1000 315 per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision</td>
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<tr>
<td>ICU admission</td>
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<tr>
<td>Demographic</td>
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<tr>
<td>Male vs female</td>
<td>19 (3)</td>
<td>2.87 (0.29 to 28.27)</td>
<td>NA per 1000 NA per 1000</td>
<td>Very low</td>
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<td>Due to very serious risk of bias and imprecision</td>
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<tr>
<td>Early disease</td>
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### Table 2 Continued

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>No of patients (studies)</th>
<th>OR (95% CI)</th>
<th>Absolute effect estimates</th>
<th>GRADE: certainty of the evidence</th>
</tr>
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<tbody>
<tr>
<td>Necrotising fasciitis vs no necrotising fasciitis</td>
<td>28 (3)</td>
<td>0.74 (0.12 to 4.48)</td>
<td>Risk without prognostic factor</td>
<td>900 per 1000</td>
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<tr>
<td>Treatment</td>
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<td>Risk with prognostic factor</td>
<td>–31 (–381 to 76)</td>
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<tr>
<td>Necrotising fasciitis vs no necrotising fasciitis</td>
<td>156 (3)</td>
<td>1.09 (0.43 to 2.77)</td>
<td>833 per 1000</td>
<td>845 per 1000</td>
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<td>IVIG versus no IVIG (all STSS patients)</td>
<td>14 (2)</td>
<td>4.60 (0.29 to 72.89)</td>
<td>500 per 1000</td>
<td>821 per 1000</td>
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<td>Any antibiotic versus no antibiotic</td>
<td>13 (2)</td>
<td>3.25 (0.21 to 50.35)</td>
<td>875 per 1000</td>
<td>958 per 1000</td>
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<tr>
<td>Haemodialysis versus no haemodialysis</td>
<td>15 (2)</td>
<td>0.86 (0.06 to 12.48)</td>
<td>NA per 1000</td>
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<tr>
<td>NSAIDs versus no NSAIDs</td>
<td>15 (2)</td>
<td>0.86 (0.06 to 12.48)</td>
<td>NA per 1000</td>
<td>NA per 1000</td>
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### Clinical cure or improvement

| Demographic | Male versus female | 23 (4) | 3.33 (0.47 to 23.59) | 875 per 1000 | 959 per 1000 | Very low |
| Treatment | | | 84 (–108 to 119) | Due to very serious risk of bias and imprecision |
| Necrotising fasciitis versus no necrotising fasciitis | 24 (2) | 0.34 (0.02 to 5.20) | 950 per 1000 | 866 per 1000 | Very low |
| IVIG versus no IVIG (in all STSS patients) | 23 (2) | 0.27 (0.02 to 3.76) | NA per 1000 | NA per 1000 | Very low |
| Haemodialysis versus no haemodialysis | 26 (3) | 1.43 (0.15 to 14.08) | NA per 1000 | NA per 1000 | Very low |

### Need for mechanical ventilation

| Demographic | Male versus female | 21 (3) | 2.09 (0.32 to 13.74) | NA per 1000 | NA per 1000 | Very low |
| Treatment | | | 120 (–200 to 440) | Due to very serious risk of bias and imprecision |
| Acute renal failure versus no acute renal failure | 20 (2) | 1.14 (0.17 to 7.82) | 750 per 1000 | 774 per 1000 | Very low |
| Necrotising fasciitis versus no necrotising fasciitis | 31 (3) | 3.75 (0.47 to 29.81) | 700 per 1000 | 897 per 1000 | Very low |

### Continued
versus no necrotising fasciitis (n=31, OR 3.75, 95% CI 0.47 to 29.81), acute renal failure versus no acute renal failure (n=20, OR 1.14, 95% CI 0.17 to 7.82), haemodialysis versus no haemodialysis (n=26, OR 2.05, 95% CI 0.39 to 10.70) and IVIG treatment versus no IVIG treatment (n=157, OR 2.22, 95% CI 0.78 to 6.32). The certainty of all need for mechanical ventilation evidence was very low due to very serious risk of bias and imprecision.

**Prognostics factors for hospital length of stay**

One prognostic factor from three studies including 201 STSS patients was eligible for analysis (table 2, online supplemental data). Low certainty evidence—due to serious risk of bias and imprecision—provides no support for an association between IVIG treatment and hospital length of stay, when compared with no IVIG treatment (n=201, MD −5.51 days, 95% CI −17.64 to 6.62).

**Prognostics factors for ICU length of stay**

One prognostic factor from two studies including 131 STSS patients was eligible for analysis (table 2, online supplemental data). We are uncertain if IVIG treatment compared with no IVIG treatment is associated with ICU length of stay (n=131, MD 3.80 days, 95% CI −3.62 to 11.23; very low certainty evidence due to very serious risk of bias and serious imprecision).

**Subgroup and sensitivity analysis**

Sparsity of data precluded our planned subgroup analyses by clindamycin treatment, presence of necrotising fasciitis and sex (ie, each subgroup did not have at least two studies). We collapsed the low and moderate risk of bias categories to allow for subgroup analysis by risk of bias (low or moderate vs high). The prognostic factor-outcome combinations for which there was sufficient evidence for subgroup analysis by age or modified risk of bias level were IVIG-mortality and sex-mortality. We found no statistical evidence that the association between IVIG and mortality differed between low or moderate and high risk of bias studies in all STSS patients (p=0.884) and clindamycin-treated STSS patients (p=0.867) or between studies with STSS patients <18 years and patients 18–64 years (p=0.328). We also found no statistical evidence that the association between sex and mortality differed between studies with patients <18 years and patients 18–64 years (p=0.666). Because results were consistent across Peto, and DerSimonian and Laird methods, our post hoc sensitivity analysis applying the Peto method supported our main results.

**DISCUSSION**

This systematic review and meta-analysis provides a comprehensive overview of the prognostic evidence for STSS. Prognostic factors for which there was a statistically significant association with mortality in STSS patients were age, clindamycin treatment, IVIG treatment and NSAIDs treatment. Patients ≥65 years compared with patients 18–64 years may have increased odds of mortality (low certainty of evidence); however, we are uncertain if the same is true for patients ≥65 years compared with patients <18 years (very low certainty of evidence). We are also uncertain whether NSAIDs increase the odds of mortality (very low certainty of evidence). Low certainty evidence suggests the odds of mortality may be reduced by treatment with clindamycin and within clindamycin-treated patients, IVIG. We are highly uncertain whether IVIG reduces mortality in all STSS patients, regardless of clindamycin treatment (very low certainty of evidence). Results failed to show a significant association between all other meta-analysed prognostic factors and outcomes (table 2). The certainty of STSS prognostic evidence was low or very low due to serious or very serious risk of bias and imprecision concerns.

Strengths of this review include its systematic and explicit search of the literature, capture of a wide breadth of patient-important outcomes within and outside of
critical care and the use of meta-analysis to increase statistical power in studying relationships between prognostic factors and outcomes in STSS patients. These strengths directly address limitations of a narrative synthesis of STSS prognosis restricted to the critical care setting. In the absence of large cohort studies and randomised trials, conclusions for STSS prognosis in this review are limited by very low to low certainty evidence. The majority of included studies were non-randomised (40/41, 98%) and small (median sample size was 11 patients), introducing bias from residual confounding and imprecision around pooled summary estimates. Small numbers of events further contributed to the imprecision around summary estimates and limited the interpretation of our findings. With few participants and events, minor changes in the data can cause major changes in the results. In such instances, results can be exaggerated by the presentation of relative effect estimates only. To minimise the risk of misinterpreting results from the inclusion of small studies in our meta-analyses, we calculated an absolute effect estimate for each relative effect estimate (table 2). Further, despite expecting small studies to be more heterogeneous than large studies, we did not find statistical evidence of heterogeneity in any of our 33 meta-analyses and in interpreting the I² statistic value, we found not likely important heterogeneity in all but one meta-analysis. Creation of an international registry of STSS patients may improve the credibility of prognostic evidence for STSS and facilitate the conduct of high-quality cohort studies. Although we meta-analysed adjusted ORs from included studies when possible, almost all included studies reported crude data (39/41, 95%), precluding adjustment for important

Figure 2  Meta-analyses comparing IVIG treatment to no IVIG treatment for the outcome mortality in (A) all STSS patients; and (B) the subset of STSS patients treated with clindamycin. Please note proportions are blank for study rows where we meta-analysed adjusted ORs instead of crude proportions. IVIG, intravenous Ig; STSS, streptococcal toxic shock syndrome.
confounders. A limitation of the evidence is the lack of long-term outcome data reported. For example, no studies quantified associations between prognostic factors and functional status or HRQoL outcomes post-infection in STSS survivors. Given the high morbidity associated with STSS, future research in STSS prognosis should quantify these patient-important outcomes, facilitating future meta-analyses and providing further insights into STSS prognosis.

Our finding that IVIG treatment may reduce the odds of mortality in STSS patients who receive clindamycin treatment is consistent with a systematic review and meta-analysis of IVIG treatment in clindamycin-treated STSS patients, which found statistical evidence of a decreased risk of mortality in IVIG-treated and clindamycin-treated STSS patients when compared with only clindamycin-treated STSS patients. For this question relevant to clindamycin-treated STSS patients, our meta-analysis included one additional non-randomised study, whose small sample size and imprecision contributed to an overall point estimate of greater magnitude. Our findings suggest that treatment regimens of IVIG in adjunct to clindamycin and clindamycin alone may significantly improve STSS prognosis. We found a significant association between a regimen of IVIG regardless of clindamycin treatment and mortality; however, due to very serious risk of bias and serious imprecision, and thus very low certainty evidence, we cannot rule out the possibility that clindamycin treatment may be necessary for STSS patients to benefit from IVIG treatment. Further, only one study reported on IVIG treatment in STSS patients that were not also treated with clindamycin; therefore, our planned subgroup analysis to test if the beneficial effect of IVIG is modified in the absence of clindamycin was precluded. Based on very low certainty evidence, our finding that NSAID treatment is significantly associated with mortality in STSS patients can be explained by clinical and basic science literature, which suggests non-selective NSAIDs mask early signs and symptoms of GAS infection, such as fever, subsequently delaying time to antibiotic treatment—a risk factor for severe sepsis and shock, and mortality.

After analysing 30 different prognostic factor and outcome combinations, we found that clindamycin treatment was significantly associated with an improved STSS prognosis. Further, we found that IVIG treatment may reduce the odds of mortality in STSS patients who receive clindamycin treatment, but we are uncertain if this is true for all STSS patients, regardless of clindamycin treatment. Although these findings support the use of IVIG as an adjunctive treatment in clindamycin-treated STSS patients, the certainty of evidence was low due to serious risk of bias and imprecision. Age equal to or older than 65 years and treatment with NSAIDs were significantly associated with a worse STSS prognosis. Results from very low to low certainty evidence failed to show a significant association between any other factors of interest and STSS prognosis.

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