The timing of use of risk stratification tools affects their ability to predict mortality from sepsis. A meta-regression analysis. [version 1; peer review: awaiting peer review]

Molly Flint¹, Fergus Hamilton², David Arnold³, Edward Carlton⁴, David Hettle⁵

¹Medical School, University of Bristol, Bristol, Somerset, UK
²Department of Infection Sciences, North Bristol NHS Trust, Bristol, Somerset, UK
³Academic Respiratory Unit, North Bristol NHS Trust, Bristol, Somerset, UK
⁴Emergency Department, North Bristol NHS Trust, Bristol, Somerset, UK

Abstract

Background: Risk stratification tools (RSTs) are used in healthcare settings to identify patients at risk of sepsis and subsequent adverse outcomes. In practice RSTs are used on admission and thereafter as ‘trigger’ tools prompting sepsis management. However, studies investigating their performance report scores at a single timepoint which varies in relation to admission. The aim of this meta-analysis was to determine if the predictive performance of RSTs is altered by the timing of their use.

Methods: We conducted a systematic review and meta-regression analysis of studies published from inception to 31 October 2018, using EMBASE and PubMed databases. Any cohort studies investigating the ability of an RST to predict mortality in adult sepsis patients admitted to hospital, from which a 2x2 table was available or could be constructed, were included. The diagnostic performance of RSTs in predicting mortality was the primary outcome. Sensitivity, specificity, positive predictive value, negative predictive value and area under the receiver-operating curve (AUROC) were the primary measures, enabling further meta-regression analysis.

Results: 47 studies were included, comprising 430,427 patients. Results of bivariate meta-regression analysis found tools using a first-recorded score were less sensitive than those using worst-recorded score (REML regression coefficient 0.57, 95% CI 0.07-1.08). Using worst-recorded score led to a large increase in sensitivity (summary sensitivity 0.76, 95% CI 0.67-0.83, for worst-recorded scores vs. 0.64
(0.57-0.71) for first-recorded scores). Scoring system type did not have a significant relationship with studies' predictive ability. The most analysed RSTs were qSOFA (n=37) and EWS (n=14). Further analysis of these RSTs also found timing of their use to be associated with predictive performance.

**Conclusion:**
The timing of any RST is paramount to their predictive performance. This must be reflected in their use in practice, and lead to prospective studies in future.

**Keywords**
Sepsis, qSOFA, Infection, EWS, Scoring, Risk stratification tool
Introduction
Background
Sepsis is a major global health issue, with 48.9 million cases per year worldwide resulting in 11 million deaths. In 2016, the SEPSIS-3 task force identified the need for “earlier recognition and more timely management”. Early detection, coupled with rapid management improves patient outcomes by reducing progression to severe sepsis, the need for intensive care unit (ICU) care, and mortality. Early detection also enables identification of those in whom a good outcome is likely, allowing more conservative management strategies. Early identification is therefore a priority, but this is challenging due to variation in clinical presentations of sepsis and the lack of a single, gold-standard diagnostic test. A variety of risk stratification tools (RSTs) are used across multiple healthcare settings to identify patients at risk of sepsis and subsequent adverse outcomes. Using physiological and biochemical parameters RSTs aim to predict patients at risk of adverse outcomes from sepsis, a deteriorating condition, or a specific infective diagnosis. Examples include: the Early Warning Score (EWS), with numerous variants; Sequential Organ Failure Assessment score (SOFA); Quick-SOFA (qSOFA); Systemic Inflammatory Response Syndrome criteria (SIRS); and organ-specific scores, such as CURB-65.

Importance
Inconsistencies in the research evidencing RSTs and their use in clinical practice potentially leads to exaggeration of their predictive ability. A major variation is in the timing of the use of RSTs. In practice RSTs are often used on admission to hospital and in the emergency department (ED) to guide management, and thereafter as trigger tools to monitor patient deterioration. However, studies investigating RSTs vary in their timing that the tool was performed in relation to admission, indeed a large number of studies use a worst-recorded score within 24–48 hours rather than reflecting the way RSTs are used in practice, which is likely to affect their reported performance.

Goals of this investigation
The primary objective of this meta-analytical study was to determine if the predictive performance of RSTs is altered by the timing of their use.

Methods
The protocol for this study was registered with PROSPERO (CRD42019146321).

Study selection and inclusion
A systematic search of EMBASE and PubMed databases from inception until October 2018 was undertaken. We aimed to include any prognostic tool identified by the search that was mainly based on physiological markers. RSTs to be included were not pre-defined, rather guided by the search strategy findings. The search identified primary research which investigated any RST used to predict mortality in adult patients (>18yo) admitted to hospital with sepsis, suspected sepsis or pneumonia. The search strategy combined terms for RSTs with terms for infection, sepsis and mortality.

Studies must have reported an RST score calculated on patients’ hospital admission or during the initial period of observation following admission for suspected infection or sepsis. Mortality was a required outcome measure of included studies, which was primarily defined as 28-day or 30-day mortality, however other mortality measures (e.g. in-hospital mortality) were accepted. Mortality was selected as the use of RSTs have been driven by campaigns such as Surviving Sepsis, advocating for early identification of septic patients to reduce mortality as far as possible. Studies in a non-ICU setting were included as several RSTs are validated for use in patients at risk of deterioration or sepsis in this setting. Studies conducted exclusively in ICU, and those investigating only trauma, paediatric, obstetric and gynaecological patients, or those with alternative diagnoses to sepsis were excluded. Language of articles was limited to English unless a translation was available. Any article that was not an observational cohort study was excluded.

Two authors (MF, DH) independently screened identified titles and abstracts using a validated web-based application, Rayyan, to produce a list of relevant articles for full-text review. Disagreements were resolved through consensus between further authors (FH, DA).

Data extraction and outcomes
The data extraction recorded: (i) RST used, (ii) timing of RST use, (iii) study design, (iv) sample size, (v) healthcare setting, (vi) geographical location, (vii) diagnosis, (viii) outcome measure for mortality, (ix) sensitivity, (x) specificity, (xi) positive predictive value, (xii) negative predictive value and (xiii) area under the receiver-operator curve (AUROC). If a study did not publish 2×2 data, this data was calculated using specificity, sensitivity, number of participants and mortality. Where studies published more than one set of 2×2 data for a single score, e.g. for multiple cut-offs, the best was taken. If identified studies investigated the use of more than one RST, all 2×2 datasets were collected and included in the analysis. Timing data was classified as ‘first recorded in ED’, ‘worst in ED’, ‘within 24 hours’, ‘within 48 hours’, or other. We then used a pragmatic approach, categorising timing further into ‘first recorded scores’, ‘worst recorded within a time point scores’ (hereafter ‘worst-recorded’) and ‘other’ for analysis. Mortality measures were coded as ‘28- or 30-day’, ‘in-hospital’ or ‘other’. As there are many Early Warning Score (EWS) variants which are all physiological scoring tools with broadly similar scoring parameters, we pragmatically cohorted these scores for analysis, allowing more powerful analysis. One author (MF) extracted data from eligible studies, which were confirmed by a second author (DH).

Risk of bias assessment
This study did not aim to include formal risk of bias assessment, as the primary objective was to quantify whether timing impacted RST performance, which itself is a major bias. All studies that used later time points would be at significant risk of bias due to the later nature of timing used (measurements occurring after diagnosis and subsequent management), and we did not feel that formally evaluating this would be helpful.
Statistical analysis
The fundamental approach taken was a meta-regression of study performance, with timing of score as the variable of interest, for all RSTs, and then for individual RSTs. All statistical analysis was performed in R 3.6.0 and 4.00, using the package mada (v 0.5.1)\textsuperscript{21}.

Initial analysis generated hierarchical summary receiver-operator characteristic (HSROC) plots, allowing for comparison of the effects of all relevant covariates across studies. Using the HSROC plots we were able to visually assess heterogeneity. We then conducted bivariate meta-regression analysis to assess the impact of the covariates on the result of the meta-analysis, the predictive ability of RSTs.

Thereafter for any RST with adequate data for analysis, bootstrapped AUC, and summary sensitivity and specificity were generated for studies investigating the effects of different timings of RST use to enable clinical comparisons. Bootstrapping was performed 1,000 times.

Results
Study characteristics
The study selection process is illustrated in Figure 1. Of the 12,853 studies identified through searches, 47 were deemed

![Figure 1. PRISMA Diagram of Evidence Search and Selection.](#)
appropriate for final inclusion, including 430,427 patients. Identified studies included a total of 113 uses of RSTs, which represented 17 different tools.

Table 1 outlines the study characteristics. The earliest study was from 2007, with the most recent published in 2018. 14 studies focussed on a single RST with 33 assessing multiple tools. The distribution of the RSTs analysed is also demonstrated in Figure 1. In terms of timing, 23 studies calculated RST score based on first recorded score, five studies reported score within 24 hours of admission, four studies reported the worst score whilst in ED, eight studies did not state when they completed a RST and seven studies used other timing scales.

Overall, 24 studies used the primarily defined outcome measure of 28- or 30-day mortality, with a further 22 using in-hospital mortality and one coded as ‘other’, using a definition of in-hospital mortality within 72 hours of admission. Average

| Lead author       | Year | n     | Mortality | Setting | Diagnostic group         | Score used | Sensitivity | Specificity | AUROC |
|-------------------|------|-------|-----------|---------|--------------------------|------------|-------------|-------------|-------|
| Chen²²            | 2018 | 69115 | 8.16%     | ED      | Suspected infection      | qSOFA      | 29%         | 92%         | 0.69  |
|                   |      |       |           |         |                          | SIRS       | 67%         | 46%         | 0.60  |
| Szakmany²³        | 2018 | 380   | 20.5%     | ED      | Suspected infection or infection | NEWS       | 41%         | 73%         | 0.59  |
|                   |      |       |           |         |                          | SOFA       | 86%         | 32%         | 0.7   |
|                   |      |       |           |         |                          | qSOFA      | 22%         | 89%         | 0.57  |
| Redondo-González²⁴ | 2018 | 349   | 21.8%     | ED      | Sepsis                   | SOFA       | 83%         | 42%         | 0.72  |
|                   |      |       |           |         |                          | qSOFA      | 65%         | 58%         | 0.67  |
|                   |      |       |           |         |                          | NEWS       | 41%         | 73%         | 0.59  |
|                   |      |       |           |         |                          | SOFA       | 86%         | 32%         | 0.7   |
|                   |      |       |           |         |                          | qSOFA      | 22%         | 89%         | 0.57  |
| Aluisio²⁵         | 2018 | 760   | 25.4%     | ED      | Infection                | qSOFA      | 86%         | 43%         | 0.70  |
| Geier²⁶           | 2013 | 151   | 14.6%     | ED      | Suspected sepsis         | qSOFA      | 86%         | 43%         | 0.70  |
|                   |      |       |           |         |                          | NEWS       | 42.9%        | 74.4%        | 0.642 |
|                   |      |       |           |         |                          | SOFA       | 86%         | 43%         | 0.70  |
|                   |      |       |           |         |                          | SIRS       | 72.1%        | 61%          | 0.72  |
|                   |      |       |           |         |                          | SOFA       | 29.7%        | 96.1%        | 0.73  |
| Quinten²⁷         | 2018 | 193   | 3.6%      | ED      | Suspected infection      | qSOFA      | 71.4%        | 84.4%        | 0.848 |
|                   |      |       |           |         |                          | NEWS       | 42.9%        | 74.4%        | 0.642 |
|                   |      |       |           |         |                          | SOFA       | 86%         | 43%         | 0.70  |
|                   |      |       |           |         |                          | SIRS       | 72.1%        | 61%          | 0.72  |
|                   |      |       |           |         |                          | SOFA       | 29.7%        | 96.1%        | 0.73  |
| Canet²⁸           | 2018 | 11205 | 4.5%      | ED      | Suspected infection      | qSOFA      | 61%         | 80%         | 0.76  |
| Williams²⁹        | 2017 | 8871  | 3.7%      | ED      | Suspected infection      | qSOFA      | 61%         | 80%         | 0.76  |
|                   |      |       |           |         |                          | SOFA       | 86%         | 43%         | 0.70  |
|                   |      |       |           |         |                          | SIRS       | 72.1%        | 61%          | 0.72  |
| Rodriguez³⁰       | 2018 | 3743  | 8.8%      | ED      | Suspected infection      | qSOFA      | 64.4%        | 83.9%        | 0.788 |
| Freund³¹          | 2017 | 879   | 8%        | ED      | Suspected infection      | qSOFA      | 73%         | 70%          | 0.77  |
|                   |      |       |           |         |                          | SOFA       | 73%         | 70%          | 0.77  |
|                   |      |       |           |         |                          | SIRS       | 93%         | 27%          | 0.65  |
| Müller³²          | 2017 | 527   | 13.3%     | ED      | Pneumonia                | qSOFA      | 26.6%        | 88.3%        | 0.587 |
|                   |      |       |           |         |                          | SIRS       | 15.7%        | 97%          | 0.497 |
|                   |      |       |           |         |                          | CURB-65    | 19.2%        | 90.9%        | 0.65  |
| Zhou³³            | 2018 | 226   | 21.68%    | ED      | Pneumonia                | SOFA       | 91.5%        | 81.6%        | 0.852 |
|                   |      |       |           |         |                          | qSOFA      | 72.3%        | 71.4%        | 0.724 |
|                   |      |       |           |         |                          | CURB-65    | 65%         | 87.8%        | 0.805 |
|                   |      |       |           |         |                          | PSI        | 83.1%        | 67.3%        | 0.81  |
| Hwang³⁴           | 2018 | 1395  | 15%       | ED      | Severe sepsis or septic shock | qSOFA     | 39%         | 77%          | 0.58  |
|                   |      |       |           |         |                          | SOFA       | 82%         | 41%          | 0.60  |
|                   |      |       |           |         |                          | qSOFA      | 91%         | 23%          | 0.57  |
| Lead author     | Year | n    | Mortality | Setting | Diagnostic group         | Score used  | Sensitivity | Specificity | AUROC  |
|-----------------|------|------|-----------|---------|--------------------------|-------------|-------------|-------------|--------|
| Shu             | 2019 | 2292 | 1.4%      | ED      | Sepsis or infection      | qSOFA       | 40.6%       | 91.9%       | NR     |
| Chen            | 2011 | 110  | 43.8%     | Ward    | Infection                | SOFA        | 67.3%       | 85.2%       | 0.845  |
|                 |      |      |           |         |                          | APAHCE II   | 75.5%       | 73.8%       | 0.806  |
| Churpek         | 2017 | 30677| 5.4%      | ED      | Suspected infection      | NEWS        | 71.9%       | 72.2%       | 0.71   |
|                 |      |      |           |         |                          | MEWS        | 71.4%       | 65%         | 0.66   |
|                 |      |      |           |         |                          | qSOFA       | 68.7%       | 63.5%       | 0.63   |
|                 |      |      |           |         |                          | SIRS        | 77.5%       | 43.8%       | 0.69   |
| Askim           | 2017 | 1535 | 2.6%      | ED      | Severe sepsis            | SIRS        | 65%         | 55%         | 0.6048 |
| Barlow          | 2007 | 419  | 19%       | Ward    | Pneumonia                | CRB-65      | 73%         | 59%         | 0.73   |
| Guirgis         | 2017 | 3297 | 10.1%     | ED      | Sepsis                   | SOFA        | 90%         | 50%         | 0.82   |
|                 |      |      |           |         |                          | qSOFA       | 38%         | 86%         | 0.68   |
| Park            | 2017 | 1009 | 15.8%     | ED      | Suspected infection      | qSOFA       | 53%         | 84%         | 0.733  |
| Wang            | 2016 | 477  | 27.5%     | ED      | Infection                | qSOFA       | 42.9%       | 82.6%       | 0.666  |
| Cildir          | 2013 | 230  | 32.2%     | ED      | Sepsis                   | MEWS        | 87.5%       | 30.4%       | 0.574  |
|                 |      |      |           |         |                          | MEWS        | 48.5%       | 67%         | 0.596  |
| Haydar          | 2017 | 200  | 11.1%     | ED      | Suspected sepsis         | qSOFA       | 90.1%       | 45.7%       | 0.68   |
|                 |      |      |           |         |                          | SIRS        | 95.5%       | 5.6%        | 0.51   |
| Tokioka         | 2018 | 1045 | 4.9%      | ED      | Pneumonia                | qSOFA       | 39.1%       | 87.8%       | 0.69   |
|                 |      |      |           |         |                          | CURB-65     | 87.5%       | 41%         | 0.75   |
|                 |      |      |           |         |                          | PSI         | 89.1%       | 42%         | 0.74   |
| van der Woude   | 2018 | 577  | 3.6%      | ED      | Infection                | MEWS        | 23.8%       | 87%         | NR     |
|                 |      |      |           |         |                          | SOFA        | 66.7%       | 79.8%       | NR     |
|                 |      |      |           |         |                          | qSOFA       | 33.3%       | 96.4%       | NR     |
|                 |      |      |           |         |                          | SIRS        | 61.9%       | 56.9%       | NR     |
| Henning         | 2017 | 7637 | 4.4%      | ED      | Suspected infection      | qSOFA       | 52%         | 86%         | 0.77   |
|                 |      |      |           |         |                          | SIRS        | 83%         | 50%         | NR     |
| Goulden         | 2018 | 1818 | 15%       | ED      | Suspected sepsis         | NEWS        | 74%         | 43%         | 0.6517 |
|                 |      |      |           |         |                          | qSOFA       | 37%         | 79%         | 0.6271 |
|                 |      |      |           |         |                          | SIRS        | 80%         | 21%         | 0.4891 |
| Raymond         | 2019 | 228  | 11%       | ED      | Suspected sepsis         | mSOFA       | 88%         | 67.5%       | NR     |
| Chof            | 2019 | 991  | 22.3%     | ED      | Sepsis                   | qSOFA       | 65.6%       | 54.8%       | 0.62   |
|                 |      |      |           |         |                          | SIRS        | 91.9%       | 11%         | 0.482  |
| Chen            | 2016 | 1641 | 33%       | ED      | Pneumonia                | qSOFA       | 53%         | 75%         | 0.655  |
|                 |      |      |           |         |                          | CRB-65      | 70%         | 57%         | 0.661  |
|                 |      |      |           |         |                          | CRB         | 36%         | 81%         | 0.651  |
| Gain            | 2019 | 323  | 7%        | Ward    | Infection                | SOFA        | 100%        | 44%         | 0.83   |
|                 |      |      |           |         |                          | qSOFA       | 38%         | 89%         | 0.67   |
|                 |      |      |           |         |                          | SIRS        | 81%         | 28%         | 0.61   |
| Lead author            | Year  | n      | Mortality | Setting | Diagnostic group       | Score used | Sensitivity | Specificity | AUROC |
|------------------------|-------|--------|-----------|---------|------------------------|------------|-------------|-------------|-------|
| González Del Castillo  | 2017  | 10776  | 6.5%      | ED      | Infection              | qSOFA      | 27.8%       | 93.7%       | 0.69  |
|                        |       |        |           |         |                        | SIRS       | 65.3%       | 49.1%       | 0.65  |
| Hifumi                 | 2016  | 171    | 17%       | Ward    | Infection              | SOFA       | 97%         | 84%         | 0.954 |
| Camm                   | 2018  | 316    | 7.91%     | ED      | Suspected infection    | NEWS       | 44%         | 73.5%       | NR    |
|                        |       |        |           |         |                        | qSOFA      | 84%         | 44.3%       | NR    |
|                        |       |        |           |         |                        | SIRS       | 56%         | 67%         | NR    |
| Rannikko               | 2018  | 481    | 14%       | ED      | Infection              | qSOFA      | 77.3%       | 77.3%       | 0.72  |
| de Groot               | 2017  | 2280   | 9.5%      | ED      | Suspected infection    | NEWS       | 63%         | 63%         | 0.67  |
|                        |       |        |           |         |                        | MEWS       | 42%         | 77%         | 0.63  |
|                        |       |        |           |         |                        | qSOFA      | 83%         | 47%         | 0.68  |
|                        |       |        |           |         |                        | PIRO       | 55%         | 77%         | 0.73  |
|                        |       |        |           |         |                        | MEDS       | 81%         | 62%         | 0.8   |
| Ranzani                | 2017  | 6024   | 6.4%      | ED      | Pneumonia              | qSOFA      | 50%         | 81%         | 0.697 |
|                        |       |        |           |         |                        | SIRS       | 89%         | 22%         | 0.579 |
|                        |       |        |           |         |                        | CURB-65    | 78%         | 60%         | 0.746 |
|                        |       |        |           |         |                        | PSI        | 92%         | 47%         | 0.78  |
|                        |       |        |           |         |                        | CRB        | 40%         | 87%         | 0.716 |
| Chen                   | 2014  | 680    | 26.2%     | ED      | Sepsis                 | CRB        | 57.9%       | 89.4%       | 0.74  |
| Lee                    | 2016  | 36     | 25%       | ED      | Sepsis                 | SOFA       | 67%         | 85%         | 0.815 |
| Huson                  | 2017  | 458    | 23%       | Ward    | Suspected infection    | qSOFA      | 72%         | 68%         | 0.73  |
| Jo                     | 2016  | 533    | 10.8%     | ED      | Pneumonia              | NEWS       | 68.3%       | 57.2%       | 0.70  |
|                        |       |        |           |         |                        | CURB-65    | 71.7%       | 52.7%       | 0.66  |
|                        |       |        |           |         |                        | PSI        | 75%         | 47.3%       | 0.68  |
| Kim                    | 2017  | 125    | 10.4%     | ED      | Pneumonia              | SOFA       | 69.2%       | 83.9%       | 0.83  |
|                        |       |        |           |         |                        | qSOFA      | 53.9%       | 89.3%       | 0.81  |
|                        |       |        |           |         |                        | CURB-65    | 53.9%       | 83.4%       | 0.77  |
|                        |       |        |           |         |                        | PSI        | 100%        | 49.1%       | 0.86  |
|                        |       |        |           |         |                        | APACHE II  | 69.2%       | 77.7%       | 0.85  |
| Tirotta                | 2017  | 526    | 14.8%     | ED      | Infection              | MEWS       | 55%         | 59%         | 0.596 |
| Vaittinada Ayar        | 2018  | 332    | 27%       | ED      | Suspected infection    | qSOFA      | 60%         | 67%         | 0.69  |
| Kofoed                 | 2008  | 151    | 5.96%     | ED      | Infection              | SOFA       | 44%         | 95%         | 0.80  |
|                        |       |        |           |         |                        | SAPS II    | 100%        | 68%         | 0.89  |
| Lafon                  | 2018  | 374    | 13%       | Ward    | Sepsis                 | qSOFA      | 74%         | 87%         | 0.8   |
| Osatnik                | 2018  | 157    | 14%       | ED      | Sepsis or infection    | qSOFA      | 63.64%      | 67.41%      | 0.65  |
|                        |       |        |           |         |                        | SIRS       | 81.8%       | 24.44%      | 0.53  |

* e-published ahead of print by October 2018
mortality of studies investigating the primary outcome of 28- or 30-day mortality was 8.57%. Extending this to all included studies with any mortality end point, mortality was 7.59%.

Study performance
There was heterogeneity in overall performance across different scoring systems across all studies, with sensitivities and specificities ranging from nearly 0 to 100, as demonstrated in Figure 2. Heterogeneity was also formally assessed by Chi-square goodness of fit (p <0.001). The summary AUC across all RSTs was 0.72 (0.70–0.74), with summary sensitivity of 0.66 (0.62–0.70), and summary specificity of 0.69 (0.64–0.74).

Meta-regression
In a bivariate analysis using timing data alone, scores using first-recorded timing were less sensitive than worst-recorded scores (REML regression coefficient 0.57 (0.07–1.08)), with a trend towards increased specificity. This corresponds to a large increase in sensitivity with later timing, with summary specificity in first-recorded RSTs of at 0.64 (0.57–0.71) compared to summary specificity of worst-recorded RSTs at 0.76 (0.67–0.83). Figure 3 demonstrates this graphically, comparing studies using first-recorded scores than those using worst-recorded scores.

In the subsequent analysis including all relevant study level covariates only three study level factors significantly impact study performance: mortality, LMIC setting, and usage of a worst-recorded timing approach (eTable 2 in the supplement). Increasing mortality in a study was associated with increased sensitivity and reduced specificity, and this was also true for studies reporting worst-recorded timings. Studies in LMIC settings also had higher specificity. No other factor (including scoring system type) was found to have a significant relationship with studies’ predictive ability.

Individual scores
For the two scores with sufficient data individually to generate meaningful outputs (qSOFA and EWS), further analysis was performed. For both these scores, a similar relationship was found between timing and study performance, although neither met statistical significance for either sensitivity or specificity, due to low study numbers.

Discussion
Summary of findings
The meta-analysis of observational cohort studies aimed to investigate whether the predictive performance of RSTs is altered by the timing of their use. Our search strategy identified 47 studies including over 430,000 patients, with qSOFA the most analysed RST. It demonstrates that the timing of performing a RST affects its predictive performance: studies utilising any RST based on first-recorded patient observations and laboratory results have a lower sensitivity than RSTs which are based on worst-recorded values in order to predict infection or sepsis-related mortality. From sub-group analysis, the effect of timing was particularly evident in studies investigating the various EWS derivatives. Alongside timing, only LMIC setting significantly impacted study performance, and no significant differences were identified between RSTs.

Clinical context
Given the global burden of sepsis, ensuring rigorous validation of the research underpinning the tools used to allow the early identification and diagnosis of patients with suspected sepsis as advocated by SEPSIS-3, is essential. Failure to do so may result in unnecessary sepsis-related morbidity and mortality. However, several criticisms have been made of RSTs’ use in sepsis, concerning the research evidencing their use and their application in clinical practice. These largely focus on either a lack of specificity or sensitivity in different settings and cohorts, and it remains clear that no one tool fully achieves a gold-standard for diagnosis. In particular, Sepsis-3 and the qSOFA score have been criticised for their largely retrospective evidence base, with variable predictive performance when investigated prospectively. Other RSTs, such as EWS, were developed to monitor patients for signs of deterioration and are increasingly used as risk-stratifying tools for deterioration of any cause in hospital inpatients, endorsed by the Royal College of Physicians and NICE. Song et al. note that there is lower predictive performance if tools such as qSOFA are completed at the initial suspicion for infection. Further, while Hamilton et al. have investigated the role of EWS in predicting sepsis-related mortality, we are not aware of other meta-analyses clearly demonstrating the critical role that timing plays in RSTs’ predictive role.

Given these challenges in the role of RSTs and in diagnosing sepsis accurately, Franchini et al. advocate for more prospective studies and outcome measures. Our study supports this, in recognising that the methods of investigating RSTs as indicators for management of sepsis must be prospective and consider predictive outcome measures, rather than the current body of evidence which is largely retrospective. Should we continue to rely on tools whose use is evidenced based on timings other than when they are used in clinical practice, that is the worst-recorded approach to researching RSTs, we risk overstating their predictive ability in identifying a condition which has potentially fatal consequences.

Limitations and strengths
There are some limitations to our work. There is wide heterogeneity between case definitions used in studies investigating RSTs’ use as well as in the mortality outcome measure reported across studies, a reflection of the likely clinical heterogeneity in our sample. This may impact the consistency of our meta-analysis, although it is not unusual to identify large amounts of heterogeneity in systematic analysis of studies investigating diagnostic test accuracy, though no clear consistent source was identified which can singly explain the heterogeneity across studies. As a meta-analysis our results may be affected by publication bias or selective reporting of datasets within included studies, however the PRISMA statement on
| CURB-65 Muller M et al | 0.19 (1.2, 0.30) |
|------------------------|------------------|
| CURB-65 Zhou H et al  | 0.05 (0.1, 0.77) |
| CURB-65 Tokoka F et al| 0.68 (0.79, 0.94) |
| CURB-65 Ranzan O et al| 0.78 (0.74, 0.82) |
| CURB-65 Jo S et al    | 0.72 (0.58, 0.82) |
| CURB-65 Kim MV et al  | 0.54 (0.30, 0.76) |
| EWS Szakmany T et al | 0.41 (0.31, 0.52) |
| EWS Redondo-Gonzalez A et al | 0.90 (0.82, 0.95) |
| EWS Geer F et al     | 0.41 (0.24, 0.61) |
| EWS Churpek MM et al | 0.72 (0.70, 0.74) |
| EWS Cidr E et al   | 0.71 (0.69, 0.74) |
| EWS Cidr E et al   | 0.49 (0.38, 0.60) |
| EWS van der et al  | 0.25 (0.12, 0.46) |
| EWS Gouden R et al | 0.74 (0.68, 0.79) |
| EWS Camm CF et al  | 0.44 (0.71, 0.63) |
| EWS de Groot et al | 0.63 (0.56, 0.69) |
| EWS de Groot et al | 0.42 (0.39, 0.49) |
| EWS Jo S et al    | 0.68 (0.55, 0.79) |
| EWS Tirola D et al | 0.55 (0.44, 0.66) |
| other Chen FC et al | 0.67 (0.65, 0.68) |
| other Geer F et al | 0.85 (0.65, 0.94) |
| other Cidr E et al | 0.72 (0.67, 0.77) |
| other Cidr E et al | 0.92 (0.84, 0.97) |
| other Muller M et al | 0.10 (0.06, 0.20) |
| other Zhou H et al | 0.83 (0.70, 0.91) |
| other Chen SJ et al | 0.74 (0.71, 0.80) |
| other Churpek MM et al | 0.77 (0.75, 0.79) |
| other Askm A et al | 0.65 (0.48, 0.77) |
| other Barlow G et al  | 0.73 (0.63, 0.82) |
| other Heyder S et al | 0.93 (0.76, 0.98) |
| other Tokoka F et al | 0.86 (0.76, 0.94) |
| other van der et al | 0.61 (0.41, 0.79) |
| other Henness DJ et al | 0.63 (0.79, 0.87) |
| other Gouden R et al | 0.80 (0.70, 0.84) |
| other Raymond NJ et al | 0.87 (0.79, 0.95) |
| other Cho A et al | 0.92 (0.87, 0.95) |
| other Chen YY et al | 0.70 (0.66, 0.74) |
| other Chen YX et al | 0.36 (0.32, 0.40) |
| other Gains S et al | 0.60 (0.50, 0.69) |
| other Gonzalez Del et al | 0.95 (0.82, 0.99) |
| other Camm CF et al | 0.55 (0.37, 0.73) |
| other de Groot et al | 0.42 (0.58, 0.62) |
| other de Groot et al | 0.81 (0.75, 0.86) |
| other Ranzan O et al | 0.69 (0.65, 0.73) |
| other Ranzan O et al | 0.69 (0.65, 0.73) |
| other Chen YX et al | 0.35 (0.30, 0.40) |
| other Jin et al     | 0.68 (0.62, 0.74) |
| other Kim MW et al | 0.95 (0.95, 0.99) |
| other Kim MW et al | 0.95 (0.95, 0.99) |
| other Kothed K et al | 0.95 (0.96, 0.99) |
| other NA et al | 0.80 (0.58, 0.91) |
| gSOFA Chen FC et al | 0.29 (0.28, 0.30) |
| gSOFA Szakmany T et al | 0.22 (0.14, 0.32) |
| gSOFA Redondo-Gonzalez A et al | 0.64 (0.53, 0.74) |
| gSOFA Alvaro AR et al | 0.43 (0.50, 0.56) |
| gSOFA Quinten VM et al | 0.71 (0.62, 0.79) |
| gSOFA Casnet E et al | 0.91 (0.67, 0.75) |
| gSOFA Williams JM et al | 0.30 (0.25, 0.35) |
| gSOFA NA | 0.64 (0.50, 0.76) |
| gSOFA Friedl Y et al | 0.70 (0.58, 0.79) |
| gSOFA Muller M et al | 0.27 (0.18, 0.39) |
| gSOFA Zhou H et al | 0.71 (0.55, 0.82) |
| gSOFA Heang SY et al | 0.39 (0.33, 0.46) |
| gSOFA Heang SY et al | 0.62 (0.70, 0.86) |
| gSOFA Hwang SY et al | 0.91 (0.86, 0.94) |
| gSOFA Shin E et al | 0.41 (0.29, 0.58) |
| gSOFA Churpek MM et al | 0.69 (0.66, 0.71) |
| gSOFA Gurgis FW et al | 0.38 (0.33, 0.43) |
| gSOFA Park HK et al | 0.53 (0.45, 0.60) |
| gSOFA Wang JF et al | 0.43 (0.36, 0.51) |
| gSOFA Hayder S et al | 0.69 (0.67, 0.70) |
| gSOFA Tokoka F et al | 0.39 (0.27, 0.53) |
| gSOFA van der et al | 0.34 (0.18, 0.55) |
| gSOFA Henning DJ et al | 0.52 (0.47, 0.57) |
| gSOFA Gouden R et al | 0.37 (0.32, 0.43) |
| gSOFA Cho A et al | 0.69 (0.59, 0.71) |
| gSOFA Chen YX et al | 0.53 (0.49, 0.57) |
| gSOFA Gains S et al | 0.40 (0.23, 0.59) |
| gSOFA Gonzalez Del et al | 0.28 (0.25, 0.31) |
| gSOFA Camm CF et al | 0.83 (0.74, 0.93) |
| gSOFA Rasmukho J et al | 0.77 (0.66, 0.86) |
| gSOFA de Groot et al | 0.63 (0.57, 0.77) |
| gSOFA Ranzan O et al | 0.50 (0.45, 0.55) |
| gSOFA Kim MW et al | 0.54 (0.39, 0.70) |
| gSOFA Vattinada Ayar et al | 0.60 (0.50, 0.69) |
| gSOFA NA et al | 0.64 (0.43, 0.81) |
| gSOFA NA et al | 0.73 (0.66, 0.83) |
| gSOFA Szakmany T et al | 0.85 (0.76, 0.92) |
| gSOFA Redondo-Gonzalez A et al | 0.82 (0.72, 0.89) |
| gSOFA Aslam H et al | 0.21 (0.05, 0.36) |
| gSOFA Freund Y et al | 0.73 (0.61, 0.82) |
| gSOFA Zhou H et al | 0.91 (0.82, 0.96) |
| gSOFA Chen SJ et al | 0.66 (0.52, 0.78) |
| gSOFA Gurgis FW et al | 0.90 (0.88, 0.93) |
| gSOFA van der et al | 0.66 (0.54, 0.75) |
| gSOFA Gains S et al | 0.98 (0.83, 1.00) |
| gSOFA Hilmire T et al | 0.95 (0.81, 0.99) |
| gSOFA Lee WJ et al | 0.65 (0.35, 0.86) |
| gSOFA Kim MW et al | 0.68 (0.42, 0.86) |
| gSOFA Kofoid K et al | 0.45 (0.20, 0.73) |
Figure 2. Forest plots summarising the sensitivity and specificity in analysed RSTs.
Figure 3. Comparison of studies using first-recorded timings versus studies using worst-recorded timings.

meta-analysis of diagnostic test accuracy studies concluded that there is less risk of these biases than in reviews of primary interventional studies, as well as no adequately powered statistical test for a comprehensive assessment of bias in studies such as ours. Risk of bias assessment is challenging in this setting, as a major bias in all studies is that physiological responses change with treatment. As such, all studies that used later time points are at significant risk of bias, which is the focus of this study. Having said that the strengths of our study lie primarily in the use of a comprehensive search strategy across multiple databases, resulting in a large cohort of 430,427 patients being included in the final analysis. Using this large cohort and bivariate random effects analysis we hope to have minimised biases often present in observational cohorts, allowing the construction of HS-ROC curves. The large number of identified studies also allowed sub-group analysis of qSOFA and EWS in further detail, delivering greater insight into their use as RSTs and the impact of timing. Though there is suspicion regarding the lack of high-quality prospective studies investigating RSTs’ use, that this analysis includes a significant number of prospective studies reinforces that these findings are likely generalisable to either mode of study design.

Implications for Clinical Practice and Research

Our findings outline that clinicians must recognise that the performance of any RST is largely related to when they are used, not the individual tool. Given the low specificity of first-recorded RSTs and the impact that research driven by worst-recorded scores has had on policy design in potentially infected or septic patients, leading to the wide used of RSTs worldwide, there must be more prospective studies investigating their role and predictive value aligned with their use in practice: at the point of admission, or first suspicion of infection. In most settings, where infection and sepsis are priorities and the threat of antibiotic resistance looms large, failure to investigate the RSTs evidencing early management and antibiotic administration could lead to inaccurate identification of patients at risk of sepsis and inappropriate use of antimicrobials.
This project contains the following underlying data:

- Author link.csv
- Data additions.docx

### Conclusion
In summary, we must be rigorous in ensuring that the tools and scores used to predict sepsis-related mortality, and enable management and treatment decisions are used and evidenced appropriately. It remains challenging to determine how effective RSTs are in this role, as the timing of RSTs’ use in the evidence base is varied, often reflecting a worst-recorded in a time point approach, unlike their use in clinical practice. This meta-analysis has shown that the timing of RSTs is paramount to their predictive performance. This has important implications for their use in practice and stresses the importance of prospective studies in the future.

### Data availability

**Underlying data**

Underlying Data for “The timing of use of clinical screening tools affects their ability to predict sepsis mortality. A meta-regression analysis.” DOI: https://doi.org/10.5281/zenodo.5519552

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

### Authors’ contributions

DH, FH and DA conceived the idea. MF, DH and FH undertook abstract screening and data extraction. FH, DA and EC acted as content experts in the field of sepsis and RSTs. MF and DH drafted the manuscript and all authors contributed to its editing and revision. All authors interpreted data and approved the final version of the manuscript.

### Acknowledgements

We would like to thank Sarah Rudd, MSc, North Bristol NHS Trust clinical librarian for assistance in conducting the literature searches.

### References

1. World Health Organisation: Sepsis. 2018; [updated 19 April 2018].
   Reference Source

2. Rudd KE, Johnson SC, Aages K, et al.: Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020; 395(10219): 200–11.
   PubMed Abstract | Publisher Full Text | Free Full Text

3. Angus DC, Linde-Zwirble WT, Lidicker J, et al.: Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001; 29(7): 1368–77.
   PubMed Abstract | Publisher Full Text | Free Full Text

4. Singer M, Deutschman CS, Seymour CW, et al.: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315(8): 801–10.
   PubMed Abstract | Publisher Full Text | Free Full Text

5. Rivers E, Nguyen B, Havstad S, et al.: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345(19): 1368–77.
   PubMed Abstract | Publisher Full Text | Free Full Text

6. Nguyen HB, Corbett SW, Steele R, et al.: Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. Crit Care Med. 2007; 35(4): 1105–12.
   PubMed Abstract | Publisher Full Text

7. Seymour CW, Gesten F, Prescott HC, et al.: Time to Treatment and Mortality during Manded Emergency Care for Sepsis. N Engl J Med. 2017; 376(23): 2235–44.
   PubMed Abstract | Publisher Full Text | Free Full Text

8. Rhodes A, Evans LE, Alhazzani W, et al.: Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017; 43(3): 304–77.
   PubMed Abstract | Publisher Full Text

9. Goulten R, Hoyle MC, Monis J, et al.: qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. Emerg Med J. 2018; 35(6): 435–49.
   PubMed Abstract | Publisher Full Text

10. Hamilton F, Arnold D, Baird A, et al.: Early Warning Scores do not accurately predict mortality in sepsis: A meta-analysis and systematic review of the literature. J Infect. 2018; 76(3): 241–8.
    PubMed Abstract | Publisher Full Text

11. Carrigan SD, Scott G, Tabrizian M: Toward resolving the challenges of sepsis diagnosis. Clin Chem. 2004; 50(8): 1301–14.
    PubMed Abstract | Publisher Full Text

12. Song JJ, Sin CK, Park HK, et al.: Performance of the quick Sequential (sepsis-related) Organ Failure Assessment score as a prognostic tool in infected patients outside the intensive care unit: a systematic review and meta-analysis. Crit Care. 2018; 22(1): 28.
    PubMed Abstract | Publisher Full Text | Free Full Text

13. Alam N, Hobbeltin EL, van Tienhoven AJ, et al.: The impact of the use of the Early Warning Score (EWS) on patient outcomes: a systematic review. Resuscitation. 2014; 85(5): 587–94.
    PubMed Abstract | Publisher Full Text | Free Full Text

14. National Institute of Clinical Excellence: Sepsis: Recognition, Diagnosis and Early Management. London: NICE; 2016.
    Reference Source

15. NHS England: National Early Warning Score (NEWS). 2019.
    Reference Source

16. Levy MM, Fink MP, Marshall JC, et al.: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003; 29(4): 530–8.
    PubMed Abstract | Publisher Full Text

17. National Institute of Clinical Excellence: Pneumonia in adults: diagnosis and management. In: Health, editor. 2014.
    Reference Source

18. Hwang SY, Jo IJ, Lee SU, et al.: Low Accuracy of Positive qSOFA Criteria for Predicting 28-Day Mortality in Critically Ill Sepsic Patients During the Early Period After Emergency Department Presentation. Ann Emerg Med. 2018; 71(1): 1–9.e2.
    PubMed Abstract | Publisher Full Text

19. Moskowitz A, Andersen LW, Cocchi M, et al.: The Misapplication of Severity-of-Illness Scores toward Clinical Decision Making. Am J Respir Crit Care Med. 2016; 194(3): 256–8.
    PubMed Abstract | Publisher Full Text

20. Ouzzani M, Hammady H, Fedorowicz Z, et al.: Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016; 5(1): 210.
    PubMed Abstract | Publisher Full Text | Free Full Text
21. Doebler F, Holling H: Meta-analysis of diagnostic accuracy with mada. 

22. Reference Source

23. Chen FC, Kung CT, Cheng HH, et al.: Quick Sepsis-related Organ Failure Assessment predicts 72-h mortality in patients with suspected infection. Eur J Emerg Med 2019; 26(5):223-8. 

PubMed Abstract | Publisher Full Text | Free Full Text

24. Szakmany T, Pugh R, Kopczynska M, et al.: The prognostic performance of qSOFA for community-acquired pneumonia. J Intensive Care 2018; 6: 46. 

PubMed Abstract | Publisher Full Text | Free Full Text

25. Aluisio AR, Garberer S, Wiskel T, et al.: Mortality outcomes based on ED qSOFA score and HIV status in a developing low income country. Am J Emerg Med. 2018; 36(11): 2010-9. 

PubMed Abstract | Publisher Full Text | Free Full Text

26. Geier F, Popp S, Greve Y, et al.: Severity illness scoring systems for early identification and prediction of in-hospital mortality in patients with suspected sepsis presenting to the emergency department. Wien Klin Wochenschr. 2018; 130(17–18): 508-15. 

PubMed Abstract | Publisher Full Text | Free Full Text

27. Quinten VM, van Meurs M, Wolfensperger AE, et al.: Sepsis patients in the emergency department: stratification using the Clinical Impression Score, Predisposition, Infection, Response and Organ dysfunction score or quick Sequential Organ Failure Assessment? Emerg Med J. 2018; 35(5): 328-34. 

PubMed Abstract | Publisher Full Text | Free Full Text

28. Canet E, Taylor OM, Khor R, et al.: qSOFA as predictor of mortality and prolonged ICU admission in Emergency Department patients with suspected infection. J Crit Care. 2018; 48: 118-23. 

PubMed Abstract | Publisher Full Text

29. Williams JM, Greenslade JH, McKenzie JV, et al.: Systemic Inflammatory Response Syndrome, Quick Sequential Organ Function Assessment, and Organ Dysfunction: Insights From a Prospective Database of ED Patients With Infection. Chest. 2017; 151(3): 586-96. 

PubMed Abstract | Publisher Full Text

30. Rodriguez RM, Greenwood JC, Nuckton TJ, et al.: Comparison of qSOFA with current emergency department tools for screening of patients with sepsis for critical illness. Emerg Med J. 2018; 35(6): 350-6. 

PubMed Abstract | Publisher Full Text

31. Freund Y, Lemachatti N, Krasinova E, et al.: Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. JAMA. 2017; 317(3): 301-8. 

PubMed Abstract | Publisher Full Text

32. Muller M, Guignard V, Schefold JC, et al.: Utility of quick sepsis-related organ failure assessment (qSOFA) to predict outcome in patients with pneumonia. PLoS One. 2017; 12(12): e0188913. 

PubMed Abstract | Publisher Full Text | Free Full Text

33. Zhou H, Guo S, Tan T, et al.: Risk stratification and prediction value of procalcitonin and clinical severity scores for community-acquired pneumonia in ED. Am J Emerg Med. 2018; 36(12): 2155-60. 

PubMed Abstract | Publisher Full Text

34. Zhou H, Ives T,upaten C, Frye W, et al.: Pre-hospital qSOFA as a predictor of sepsis and mortality. Am J Emerg Med. 2019; 37(7): 1273-8. 

PubMed Abstract | Publisher Full Text

35. Chen SJ, Chao TF, Chiang MC, et al.: Prediction of patient outcome from Acinetobacter baumannii bacteremia with Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Intem Med. 2011; 50(8): 871-7. 

PubMed Abstract | Publisher Full Text

36. Churpek MM, Snyder A, Han X, et al.: Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit. J Aer Med. 2017; 190(7): 906-11. 

PubMed Abstract | Publisher Full Text | Free Full Text

37. Am J, Moser F, Gustad LT, et al.: Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality - a prospective study of patients admitted with infection to the emergency department. Scand J Trauma Resusc Emerg Med. 2017; 25(1): 56. 

PubMed Abstract | Publisher Full Text | Free Full Text

38. Barlow G, Nathwani D, Davey P: The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia. Thorax. 2007; 62(5): 253-9. 

PubMed Abstract | Publisher Full Text | Free Full Text

39. Guirgis FW, Puskarich MA, Smotherman C, et al.: Development of a Simple Sequential Organ Failure Assessment Score for Risk Assessment of Emergency Department Patients With Sepsis. J Intern Med. 2020; 35(3): 270-278. 

PubMed Abstract | Publisher Full Text | Free Full Text

40. Park HK, Kim WY, Kim MC, et al.: Quick sequential organ failure assessment compared to systemic inflammatory response syndrome for predicting sepsis in emergency department. J Crit Care. 2017; 42: 12-7. 

PubMed Abstract | Publisher Full Text

41. Wang JY, Chen YX, Guo SB, et al.: Predictive performance of quick Sepsis-related Organ Failure Assessment for mortality and ICU admission in patients with infection at the ED. Am J Emerg Med. 2016; 34(9): 1788-93. 

PubMed Abstract | Publisher Full Text

42. Cillard E, Bulut M, Akilin H, et al.: Evaluation of the modified MEDS, MEWS score and Charlson comorbidity index with community acquired sepsis in the emergency department. Intern Emerg Med. 2013; 8(3): 255-60. 

PubMed Abstract | Publisher Full Text

43. Haydar S, Spanier M, Weemps P, et al.: Comparison of qSOFA score and SIRS criteria as screening mechanisms for emergency department sepsis. Am J Emerg Med. 2017; 35(11): 1730-3. 

PubMed Abstract | Publisher Full Text | Free Full Text

44. Tokioka F, Okamoto H, Yamazaki A, et al.: The prognostic performance of qSOFA for community-acquired pneumonia. J Intensive Care. 2018; 6: 46. 

PubMed Abstract | Publisher Full Text | Free Full Text

45. van der Woude SW, van Doormaal FF, Hutten BA, et al.: Classifying sepsis patients in the emergency department using SIRS, qSOFA or MEWS. Neth J Med. 2018; 76(4): 158-66. 

PubMed Abstract

46. Henning DJ, Puskarich MA, Self WH, et al.: An Emergency Department Validation of the SEP-3 Sepsis and Septic Shock Definitions and Comparison With 1992 Consensus Definitions. Am J Emerg Med. 2017; 37(4): 544-52.e5. 

PubMed Abstract | Publisher Full Text | Free Full Text

47. Gouden R, Hoyle MC, Monis J, et al.: qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. Emerg Med J. 2018; 35(6): 505-9. 

PubMed Abstract | Publisher Full Text

48. Raymond NJ, Nguyen M, Allmark S, et al.: Modified Sequential Organ Failure Assessment sepsis score in an emergency department setting: Retrospective assessment of prognostic value. Emerg Med Australas. 2019; 31(3): 339-46. 

PubMed Abstract | Publisher Full Text

49. Gainis S, Relister MM, Pedersen C, et al.: Prediction of 28-days mortality with sequential organ failure assessment (SOFA), quick SOFA (qSOFA) and systemic inflammatory response syndrome (SIRS) - A retrospective study of medical patients with acute infectious disease. Int J Infect Dis. 2019; 78: 1-7. 

PubMed Abstract | Publisher Full Text

50. Gonzalez Del Castillo J, Julian-Jimenez A, Gonzalez-Martinez F, et al.: Prognostic accuracy of SIRS criteria, qSOFA score and GYM score for 30-day mortality in older non-severely dependent infected patients attended in the emergency department. Eur J Clin Microbiol Infect Dis. 2017; 36(12): 2361-9. 

PubMed Abstract | Publisher Full Text

51. Hilfmit T, Fujishima S, Abe T, et al.: Prognostic factors of Streptococcus pneumoniae infection in adults. Am J Emerg Med. 2016; 34(6): 202-6. 

PubMed Abstract | Publisher Full Text

52. Cramm CF, Hayward G, Elias TCN, et al.: Sepsis recognition tools in acute ambulatory care: associations with process of care and clinical outcomes in a service evaluation of an Emergency Multidisciplinary Unit in Oxfordshire. BMJ Open. 2018; 8(4): e020497. 

PubMed Abstract | Publisher Full Text | Free Full Text

53. Ramnikko A, Senkat T, Huttunen R, et al.: Plasma cell-free DNA and qSOFA score predict 7-day mortality in 481 emergency department bacteriaemia patients. Intern Emerg Med. 2017; 284(4): 418-26. 

PubMed Abstract | Publisher Full Text | Free Full Text

54. de Groot B, Stolwijk F, Warmenard M, et al.: The most commonly used disease severity scores are inappropriate for risk stratification of older emergency department sepsis patients: an observational multi-centre study. Scand J Trauma Resusc Emerg Med. 2017; 15(3): 91. 

PubMed Abstract | Publisher Full Text | Free Full Text

55. Ranzani OT, Prina E, Menendez R, et al.: New Sepsis Definition (Sepsis-3) and Community-acquired Pneumonia Mortality: A Validation and Clinical Decision-Making Study. Am J Resp Crit Care Med. 2017; 196(10): 1287-97. 

PubMed Abstract | Publisher Full Text

56. Chen YY, Li CS: Arterial lactate improves the prognostic performance of qSOFA score in septic patients in the ED. J Aer Med. 2014; 35(9): 982-6. 

PubMed Abstract | Publisher Full Text

57. Lee WJ, Woo SH, Kim DH, et al.: Are prognostic scores and biomarkers such as procalcitonin the appropriate prognostic precursors for elderly patients compared to systemic inflammatory response syndrome for predicting sepsis in emergency department. J Aer Med. 2014; 35(9): 982-6. 

PubMed Abstract | Publisher Full Text

58. Publisher Full Text
