Title page

Tamas Szakmany[1,2,*], Richard Pugh[3], Maja Kopczynska[1], Robert Michael Lundin[1], Ben Sharif[1], Paul Morgan[4], Gemma Ellis[1,4], Julimar Abreu[1], Svetlana Kulikouskaya[1], Kiran Bashir[1], Luke Galloway[1], Haamed Al-Hassan[1], Thomas Grother[1], Paul McNulty[1], Steffan Treharne Seal[1], Alice Cains[1], Margriet Vreugdenhil[1], Mustafa Abdimalik[1], Naomi Dennehey[1], Georgina Evans[1], Jasmine Whitaker[1], Elizabeth Beasant[1], Charles Hall[1], Maria Lazarou[1], Chloe Victoria Vanderpump[1], Kate Harding[1], Leo Duffy[1], Abigail Guerrier Sadler[1], Rachel Keeling[1], Charldre Banks[1], Stephanie Wai Yee Ng[1], Sieh Yen Heng[1], Daniah Thomas[1], Elen Wyn Puw[1], Igor Otahal[5], Ceri Battle[6], Orsolya Minik[7], Ronan A Lyons[8], Judith E Hall[1] on behalf of the Welsh Digital Data Collection Platform Collaborators[9]

Defining sepsis on the wards: results of a multi-centre point-prevalence study comparing two sepsis definitions

[1]Department of Anaesthesia, Intensive Care and Pain Medicine, Division of Population Medicine, Cardiff University, Heath Park Campus, Cardiff, CF14 4XN, UK
[2]Anaesthetic Directorate, Aneurin Bevan University Health Board, Royal Gwent Hospital, Cardiff Road, Newport, Gwent, NP20 2UB, UK
[3]Anaesthetic Department, Glan Clywdd Hospital, Betsi Cadwaladar University Health Board, Rhuddlan Road, Bodelwyddan, Rhyl, LL18 5UJ, UK
[4]Critical Care Directorate, University Hospital of Wales, Cardiff and Vale University Health Board, Heath Park Campus, Cardiff, CF14 4XN, UK
[5]Anaesthetic Department, Glangwili General Hospital, Hywel Dda University Health Board, Dolgwili Road, Carmarthen, SA31 2AF, UK
[6]Critical Care Directorate, Morriston Hospital, Abertawe Bro Morgannwg University Health Board, Heol Maes Eglwys, Swansea, SA6 6NL, UK

[7]ACT Directorate, Royal Glamorgan Hospital, Cwm Taf University Health Board, Ynysmaerdy, Llantrisant, CF72 8XR, UK

[8]Farr Institute, Swansea University Medical School, Data Science Building, Singleton Park, Swansea, SA2 8PP

[9]Membership of the Welsh Digital Data Collection Platform Collaborators is provided in the Appendix

Corresponding author:

Dr Tamas Szakmany MD, PhD, EDIC, DESA, FRCA, FFICM

Senior Lecturer in Intensive Care, Department of Anaesthesia, Intensive Care and Pain Medicine, Division of Population Medicine, Cardiff University, Heath Park Campus, Cardiff, CF14 4XN, UK

Tel: +442920723112

e-mail: szakmanyt1@cardiff.ac.uk

Summary

Our aim was to prospectively determine the predictive capabilities of SEPSIS-1 and SEPSIS-3 definitions in the Emergency Departments and general wards. Patients with National Early Warning Score of 3 or above and suspected or proven infection were enrolled over a 24-hour period in 13 Welsh hospitals. Primary outcome was mortality within 30 days.

Out of the 5422 patients screened, 431 fulfilled inclusion criteria and 380 (88%) were recruited. Using the SEPSIS-1 definition 212 patients had sepsis. Using the SEPSIS-3 definitions with Sequential Organ Failure Assessment score ≥2, 272 patients, with quickSOFA score ≥2, 50 patients were identified. For the prediction of primary outcome SEPSIS-1 criteria had a sensitivity (95%CI) 65% (54%-75%) and specificity (95%CI) 47% (41%-53%), SEPSIS-3 criteria had a sensitivity (95%CI) 86% (76%-92%) and specificity (95%CI) 32% (27%-38%). SEPSIS-3 and SEPSIS-1 definitions were associated with an HR of 2.7 (95% CI, 1.5-5.6) and HR of 1.6 (95% CI, 1.3-2.5), respectively. Scoring system discrimination evaluated by receiver operating characteristic curves was highest for Sequential Organ Failure Assessment score (0.69 [95% CI 0.63-0.76]), followed by National Early Warning Score (0.58 [0.51-0.66]) (p-value <0.001). Systemic Inflammatory Response Syndrome criteria (0.55 [95%CI 0.49-0.61]) and quickSOFA score (0.56 [95%CI 0.49-0.64]) could not predict outcome. SEPSIS-3 definition identified patients with the highest risk. Sequential Organ Failure Assessment score and National Early Warning Score were better predictors of poor outcome.

Sequential Organ Failure Assessment score appeared to be the best tool for identifying patients with high risk of death and sepsis induced organ dysfunction.

Keywords: sepsis; SOFA; NEWS; mortality; qSOFA; SIRS

Word count 2978

Introduction

Sepsis is defined as dysregulated host response to infection, resulting in acute organ dysfunction [1]. While the condition has been thoroughly studied in the Intensive Care Unit (ICU), accurate data collection outside of this setting is less well-developed. It is thought however that the number of cases in the wider hospital is far higher [2-4]. In the UK, anaesthetists and critical care practitioners have been at the forefront of developing effective systems to identify and treat patients with sepsis outside the critical care areas. They identified a clear need to understand the significance of the condition in the pre-ICU environment and the tools we might use to identify and treat those most at risk [5].

We previously reported the results of a point prevalence feasibility study and subsequent study of all Welsh centres using the 1992 International Consensus Criteria for sepsis (SEPSIS-1) utilsing electronic data collection and real-time data monitoring [6-8] We found that four percent of hospitalised patients had sepsis, half of whom had significant organ dysfunction (severe sepsis). Strikingly, the 90-day mortality among the whole hospital cohort was in excess of 30% for sepsis and almost 40% for severe sepsis [7].

Concurrently, the validity and clinical utility of the existing sepsis definitions, which were previously based on the concept of systemic inflammatory response syndrome (SIRS) were questioned [9]. The 3rd International Consensus Definitions for sepsis (SEPSIS-3) have recently been published, with significantly

revised clinical criteria, including the use of Sequential Organ Failure Assessment (SOFA) scores and the quick SOFA (qSOFA) screening tool for non-ICU settings [1, 10]. During the development phase, most of the datasets used were from North America including variable proportions of non-ICU patients [10]. It is not known how the new SEPSIS-3 definitions would perform compared with SEPSIS-1 definitions in identifying patients at risk with sepsis in a UK ward setting, and furthermore how they might perform compared with a well-established track and trigger tool, the National Early Warning Score (NEWS) [11, 12].

Our objectives were to determine the ability of the SEPSIS-1 definition using the SIRS criteria, the SEPSIS-3 definition using SOFA and qSOFA scores and the NEWS track and trigger tool to predict outcome outside of the ICU.

Methods

This multi-centre, prospective, observational study of patients with suspected sepsis in 13 hospitals in Wales was approved by the South Wales Regional Ethics Committee (16/WA/0071) and patients or their proxy in case of patients lacking capacity gave written informed consent. We enrolled consecutive patients presenting to hospitals in Wales with 24/7 consultant-level Emergency Department (ED) supervision and the facility to admit and treat any acutely unwell patient. We screened patients in.the ED or in an acute in-patient ward setting with suspected or proven infection on 19th October 2016, Wednesday (0800 to 0759 hours the following day). This date represented a typically "average" day in the NHS [13,14]. We approached all patients with NEWS≥3 in whom the treating clinical teams had a high clinical suspicion of an infection (documented as such in the medical or nursing notes) and following consent we screened for presence of sepsis either using SEPSIS-1 or SEPSIS-3 definitions. We excluded patients if they were less than 18 years of age or if they were already on intensive care or high dependency units. We referred patients to the clinical teams if the medical student data collectors felt they needed urgent medical attention due to their condition, in line with the requirements of the Ethics approval. To facilitate linkage to national databases for the collection of follow-up data, we collected patient identifiable data and entered on to the secure data collection tool.

We defined sepsis as presence or strong suspicion of infection together with 2 or

more SIRS criteria according to the SEPSIS-1 definition or as presence or strong suspicion of infection together with SOFA score 2 or above, or qSOFA score 2 or above according to the SEPSIS-3 definition. We used SIRS criteria as (respiratory rate greater than 20 breaths per minute, temperature greater than 38° C or less than 36° C, heart rate greater than 90 beats per minute, and white blood cell count greater than 12,000/mm3, less than 4,000/mm3, or greater than 10% bands) [6]. We defined qSOFA scores as systolic blood pressure ≤100mm Hg, respiratory rate ≥22 breaths per minute, and altered mental status (defined as either a Glasgow Coma Scale score ≤13 or an Alert Voice Pain Unresponsive scale (AVPU) other than “Alert”) [10]. We calculated SOFA and NEWS scores based on previously published tables [11, 15].

To calculate SOFA scores and determine organ dysfunction according to the SEPSIS-1 definition, we used laboratory values within 24 hours of study enrolment, and if no prior values were available a median (normal) value was imputed, as per prior studies [3, 10, 16]. Most patients did not have an arterial blood gas available at time of observation, so to calculate the respiratory component of the SOFA score, we followed the algorithm developed and validated by Pandharipande and colleagues [16]. We defined infection related acute organ dysfunction according to the SEPSIS-1 criteria as any of the following present: systolic BP <90 mmHg or MAP < 65 mmHg or lactate > 2.0 mmol/L (after initial fluid challenge), INR >1.5 or aPTT >60 s, Bilirubin >34 µmol/L, Urine output <0.5 mL/kg/h for 2 h, Creatinine >177 µmol/L, Platelets <100 ×109/L, PaO2/FiO2 ratio below 250, or as SOFA score 2 or above

according to the SEPSIS-3 definition [1, 6]. We recorded the NEWS score on study entry and we noted if this was the worst value in the preceding 24-hour period. [10, 15]

Data collectors, working in pairs to ensure data validity and appropriate clinical knowledge, were supported by continuous online web-chat. This ensured that senior clinicians identified through the Welsh Intensive Care Society Audit and Research Group and three study coordinators were available throughout the trial period. We provided key study information through e-mails, face-to-face training and online video tutorials, which included the protocol, answers to key questions and description of the electronic case report form (eCRF) on the electronic tablets. We previously published the details of the digital data collection platform developed for this study [8].

We collected data from medical and nursing records, including demographic data, baseline co-morbidity and frailty (according to the Dalhousie Clinical Frailty Scale), physiological and laboratory values and process measures (such as critical care involvement and completion of sepsis care bundles) [17]. We followed up patients until 30 days after study enrolment.

Outcomes

The primary outcome was mortality within 30 days of recruitment. Secondary outcome was presence of organ dysfunction defined by SOFA score >2 or presence of “severe sepsis” according to the SEPSIS-1 definition [10, 18].

Statistical analysis:

Categorical variables are described as proportions and are compared using chi-square or Fisher's exact test. Comparisons of continuous variables are performed using one-way ANOVA or Mann-Whitney test as appropriate.
To assess the performances of the SEPSIS-1 and SEPSIS-3 definitions to predict the primary end point, we calculated diagnostic performances (sensitivity, specificity, negative and positive predictive values). We constructed a receiver operating characteristic (ROC) curve and calculated the corresponding area under the ROC curve (AUROC). We plotted Kaplan-Meier survival curves and compared time-to-event data using log-rank test. We estimated the respective hazard ratios (HRs) for the primary outcome within 30 days of SEPSIS-1 and SEPSIS-3 definitions with a Cox proportional hazards model after adjustment for measured confounders. The model fit was assessed by the -2 log likelihood statistics and Chi-square test. All statistical tests were calculated using SPSS 20.0 (SPSS Inc., Chicago, IL). A two-tailed p-value <0.05 was considered statistically significant.

Results:

There were 5422 in-patients in the 24-hour study period in the 13 participating hospitals (Fig 1). 431 patients had NEWS≥3 and documented clinical suspicion of infection and all were approached for recruitment. Sixty-four patients (16.8%) were recruited in the ED, the others in a variety of ward-based environments. Baseline characteristics are summarised in Table 1.

We identified 212 patients having sepsis using the SEPSIS-1 definition, and 272 patients using the SEPSIS-3 definition with SOFA≥2 (Fig 2)., Using the qSOFA, 50 fulfilled the definition criteria (Fig 2). Out of the cohort of 380 patients, 44 fulfilled neither the SEPSIS-1 nor the SEPSIS-3 criteria (Fig 2). We present the characteristics of these groups and secondary outcomes in Online resource Table 1. Sepsis related organ dysfunction ("severe sepsis") was present in 124 out of 212 patients (58.5%) according to SEPSIS-1 criteria. 99/124 (79.8%) patients had SOFA≥2 and 24/124 (19.4%) had qSOFA≥2.
Out of the 272 patients with sepsis using the SEPSIS-3 definition, 183 (67.3%) fulfilled "severe sepsis" criteria. 232/272 (85.3%) of patients had SOFA≥2 using only basic physiological (respiratory, cardiovascular and neurological) parameters.

SEPSIS-1 and SEPSIS-3 definitions identified various proportions of the 78/380 (20.5%) patients who died within 30 days (Fig 3). We found a statistically

significant difference in the survival of patients described by the SEPSIS-1 and SEPSIS-3 definitions or meeting both criteria (Fig 4).

We report the predictive performances of SEPSIS-1 and SEPSIS-3 definitions in Table 2 and Online resource Fig 1.

After adjustment for age and presence of heart failure and using a Cox model, we found that the SEPSIS-3 definition was associated with death with an HR of 2.7 (95% CI, 1.5-5.6). The previous SEPSIS-1 definition had an HR of 1.6 (95% CI, 1.03-2.5).

Scoring system discrimination for the primary outcome was highest for SOFA (AUROC 0.70 [95% CI 0.63-0.77], p<0.001), followed by NEWS (AUROC 0.59 [0.51-0.66], p=0.02) Positive likelihood ratio was 1.27 (95%CI 1.13-1.43) for SOFA and 1.48 (95%CI 1.02-2.16) for NEWS. Negative predictive value for SOFA was 89% (95%CI, 81%-94%) and for NEWS 73% (95% CI, 67%-77%). SIRS (AUROC 0.55 [95%CI 0.48-0.62]) and qSOFA score (AUROC 0.57 [95%CI 0.49-0.64]) could not statistically predict outcome in this patient population (p=0.21 and 0.07 for SIRS and qSOFA, respectively). We report the predictive capabilities of qSOFA≥2, severe sepsis criteria defined by the SEPSIS-1 definition and NEWS≥6 in Table 2.

Prognostic performances of SOFA, qSOFA, SIRS and NEWS to predict acute organ dysfunction are reported in Online resource Table 2 and Online resource

Fig 2. SOFA was the best predictive model (AUROC 0.950 [95%CI 0.930-0.971], p<0.001), followed by NEWS (AUROC 0.694 [95%CI 0.634-0.754], p<0.001), qSOFA (AUROC 0.668 [95%CI 0.606-0.730], p<0.001) and SIRS (AUROC 0.580 [95%CI 0.514-0.647], p=0.029).

Fifty-nine patients (15.5%) were screened for sepsis using the official All Wales sepsis screening tool. Sepsis-6 bundle was completed in 44 occasions (11.6%), Critical care outreach was involved in 33 cases (8.7%). Intravenous antibiotics were administered either as a mono- or a combination-therapy to 220 (57.9%) patients.

Discussion:

To our knowledge this is the first prospective evaluation of the diagnostic and predictive capability of SEPSIS-1 versus SEPSIS-3 criteria in the UK. There was considerable overlap between them, SEPSIS-3 covering larger proportion of patients at risk. However, 63 (16.6%) patients - 12 of them falling into the previous “severe sepsis” category - would have been missed by applying only the new SEPSIS-3 definitions. On the other hand, application of SIRS-based criteria (SEPSIS-1) excluded 105 (27.3%) patients, all of whom had evidence of acute organ dysfunction.

Our results add further to the debate about the clinical usefulness of the qSOFA score, which was developed as an easy to use prediction tool for identifying patients at risk in the sepsis population [10]. There is an ongoing controversy surrounding the utility and efficacy of qSOFA in the prehospital, ED and general ward setting [20-24]. We found that using only the qSOFA score 50 [13.2%) patients would have been diagnosed with sepsis, missing 116 (30.5%) patients with organ dysfunction. In contrast to the results of Seymour and coworkers, qSOFA also failed to predict outcome at 30 days and did not offer any predictive value over the SOFA and NEWS scores for ability to predict infection induced acute organ failure in this patient population [10]. We found a striking disconnect between SOFA and qSOFA scores. Whilst our sample size is too small to draw firm conclusions, we have seen that the biggest discrepancy was between the

respiratory element of SOFA and qSOFA scores (data not shown). It is possible that the SpO2/FiO2 ratio used in our study is a much more sensitive parameter to indicate respiratory compromise, than the high respiratory rate in the qSOFA system. Our results warrant careful interpretation, as our sample size was orders of magnitude smaller compared to the original qSOFA study [10].

In their large dataset of non-ICU patients, median (IQR) SOFA was 1 (2), with significantly lower hospital mortality of 3% indicating a population at lower risk compared to ours. Interestingly, in their ICU cohort with a mortality of 17%, the AUROC of qSOFA at 0.66 (95%CI 0.64-0.68) was only slightly better than we have observed. Similarly, Raith and colleagues could not confirm the findings of the original paper in a patient population where the baseline risk was significantly higher with a hospital mortality of 18.7% with AUROC 0.607 (99%CI 0.603-0.611) [19]. These data suggest that qSOFA might not be a valuable tool to predict outcome in populations where the baseline risk of death is higher than 15%.

Our findings could support the use of SOFA scores even in a resource-limited ward setting, though it is unclear how this might best be integrated into already established track-and-trigger systems [10, 20, 23, 25, 26]. Donnelly and colleagues were able to show in a population based study that high admission SOFA was the best tool predict poor outcome in the hospital and within 1 year after discharge, with similar AUROC: 0.765 and HR: 2.43 (95%CI 1.84-3.21) to ours [25]. From these emerging data it is clear that SIRS based classification of sepsis is inferior compared to SOFA for delineating patient cohorts at highest risk

of poor outcome [1, 23, 25]. The exact cut-off for SOFA might need further recalibration, however the current threshold of 2 or more could be used in the vast majority of patients, by calculating the SOFA score from physiological parameters readily available at the bedside.

The high specificity and positive predictive value of NEWS≥6 for acute organ dysfunction and adverse outcome underlines the utility and importance of the current escalation protocol (“NEWS Six=Sick”) in our health care system [27]. Similar to our data, NEWS≥7 was found as the best cut-off for predicting poor outcome in a large retrospective cohort of patients with sepsis [24]. Recently a multi-centre Scottish study also found that NEWS≥6 carried an increased risk of death and ICU admission in patients admitted to the ED with sepsis [28].

Sepsis either defined by the SEPSIS-1 or SEPSIS-3 criteria had a high mortality: 22.9% of the patients died within 30 days, significantly higher than the 2.2% mortality observed in the group which did not fulfill either criteria for the diagnosis of sepsis. This was almost identical to the 22% 30-day mortality observed in our previous study, but significantly higher than the 6% and 8% mortality observed in the recent studies involving ED and ward patients [7, 20, 24]. This could probably be explained by methodological differences between studies. Churpek and colleagues used a retrospective dataset, with wider screening criteria more likely to capture patients with lower acuity [24]. In fact, only 28% of their 30677 patients met severe sepsis definition and the mortality of this subset is not reported [24]. With a focus on the ED, only 20% of patients in Freund's study met the SEPSIS-3 definition and the mortality rate is not available for this cohort [20]. In our

dataset, mortality was highest when patients met both SEPSIS-1 and SEPSIS-3 definitions, highlighting the high risk of death when infection causes end-organ dysfunction [1, 9]. On the other hand, the recent PROMISE trial in the UK recruiting patients with severe sepsis and septic shock according to the SEPSIS-1 definition reported 24.5% mortality at 28 days in the control arm, where patient characteristics were similar to our study [29]. We included all patients regardless of their “do not attempt resuscitation” status or limitation of treatment to certain levels and this could have affected mortality rates in our study.

Our results highlight the need for a simple, fast assessment tool to highlight patients on the general wards with sepsis. In the UK, anaesthetists, who will use more sophisticated clinical tools, will see many of these patients for further evaluation, but enabling the ward staff to streamline these referrals is crucial to improve processes of care.

The strengths of our work include the use of robust, previously published data collection methodology tested over subsequent studies and the wide participation of centres [7, 8]. We prospectively collected data on patients where the clinical teams suspected infection, hence we were able to test the real life utility of the new sepsis definition and proposed clinical tools and compare its performance with the already implemented SEPSIS-1 criteria. Our study has high internal validity as in our subsequent trials using similar methodology we recruited similar number of patients with almost identical outcomes in the same hospitals [7, 30].

Our study has some limitations. First, our dataset was a compromise between

being an exhaustive list of possible determinants of sepsis using different definitions, and being small enough to maintain data collector participation and data reliability. Second, we followed our patients up for only 30 days and did not collect data on cause of death. Long-term quality of life survey and health-care utilisation will be taken forward as part of a longitudinal study. Third, based on the findings of others, it is possible that we could also have missed patients with sepsis, who had NEWS below 3 (e.g. patients high temperature and white cell count, but normal respiratory rate and heart rate) [24, 31]. However, recent data suggests that NEWS≥3 may be the best trigger to screen patients for sepsis in the ED [32]. Fourth, laboratory elements of the SOFA score were missing in a number of patients: serum bilirubin in 36.3%, serum creatinine in 7.9% and platelet count in 6.3% of the cases. It is possible that due these omissions the number of patients with sepsis according to the SEPSIS-3 criteria is underrepresented in our sample. Similarly, only 33.7% of patients had their lactate measured, possibly resulting in misrepresentation of the severe sepsis category.

In conclusion, SEPSIS-3 definition identified patients with the highest risk if the full SOFA score was used, however there was a considerable overlap between the patients identified by the two definitions. SOFA and NEWS were found to be better predictors of poor outcome than qSOFA or SIRS in our population. These findings will have important implications for clinicians at the bedside and for organisations trying to improve the quality of sepsis care. For healthcare systems with established track-and-trigger mechanisms, the optimal approach to

integrating the new sepsis screening criteria with pre-existing escalation tools is yet to be determined.

Author contributions:

The Welsh Digital Data Collection Platform (WDDCP) Collaborators were entirely responsible for the study design, conduct and data analysis. Members of the writing committee had full data access and were solely responsible for data interpretation, drafting and revision of the manuscript and the decision to submit for publication. The Fiona Elizabeth Agnew Trust and the Welsh Intensive Care Society had no data access and no role in study design, conduct, analysis, or drafting this report. T . Sz. conceived the study and designed it together with J.E.H., M. K., B. S., R. M. L. and all the members of the writing committee and steering committees. Patient recruitment and data collection were performed by the members of the WDDCP collaborators (see appendix). T. Sz. and R. A. L. performed the data analysis with input from all members of the writing committee.The manuscript was drafted by T. Sz. and revised following critical review by all members of the writing committee and steering committees.

Acknowledgments

This work was supported by the Fiona Elizabeth Agnew Trust (grant number: FEATURES Award 2016) and the Welsh Intensive Care Society (grant number: Research grant 2015). The authors declare that they have no conflict of interest. The Welsh Digital Data Collection Platform Collaborators, whose names are

provided in the Appendix, completed the study.

Appendix

Membership of the Welsh Digital Data Collection Platform Collaborators is provided below:

Steering committee:

Tamas Szakmany (Chief Investigator)

Maja Kopczynska (National coordinator)

Robert Michael Lundin (National coordinator)

Ben Sharif (National coordinator)

Local coordinators:

Julimar Abreu, Svetlana Kulikouskaya, Kiran Bashir, Luke Galloway, Haamed Al-Hassan, Thomas Grother, Paul McNulty, Steffan Treharne Seal, Alice Cains, Margriet Vreugdenhil, Mustafa Abdimalik, Naomi Dennehey, Georgina Evans, Jasmine Whitaker, Elizabeth Beasant, Charles Hall, Maria Lazarou, Chloe Victoria Vanderpump, Kate Harding, Leo Duffy, Abigail Guerrier Sadler, Rachel Keeling, Charldre Banks, Stephanie Wai Yee Ng, Sieh Yen Heng, Daniah Thomas, Elen Wyn Puw, Igor Otahal, Ceri Battle, Orsolya Minik, Richard Pugh, Paul Morgan, Gemma Ellis

Ronan A Lyons (Secure Anonymous Information Linkage (SAIL) representative)

Judith E Hall

Terence Canning (Independent patient representative)

Local data collectors:

Elin Walters, Carys Durie, Robert James Hamilton Sinnerton, Benjamin Tanner, Berenice Cunningham-Walker, Chloe Spooner, Akanksha Kiran, Nabeegh

Nadeem, Vidhi Unadkat, Arwel Poacher, Sashiananthan Ganesananthan, John Ng Cho Hui, Esme Sparey, David ChunHei Li, Jessica Smith, India Corrin, Amit Kurani, Harry Waring, Adeel Khan, Claire Smith, Nicholas Doyle, Emily Baker, Abbie Shipley, Mohammad Yahya Amjad, Miriam Cynan, Nik-Syakirah Nik Azis, Imogen Hay, Catherine Russell, Joseph Davies, Rebecca Parsonson, Jude Joseph-Gubral, Ajitha Arunthavarajah, Jessica Nicholas, Aaron Harris, Jay Hale, Henry Atkinson, Jessica Webster, Tim Burnett, Josephine Raffan Gowar, Sam DeFriend, David Lawson, Charlotte Maden, Helena Jones, Hazel Preston, Nur Amirah Binti Maliki, Mark Zimmerman, Jessica Webber, Llewelyn Jones, Rebecca Phillips, Lauren McCarthy, Lara Wirt, Emily Hubbard, Emily Evans, Laura Jane Davis, Billie Atkins, Llywela Wyn Davies, Lee Sanders-Crook, Navrhinaa Vadivale, Camilla Lee, Amrit Dhadda, Sian Cleaver, Genna Logue, Joy Inns, Isabel Jones, Robyn Howcroft, Carys Gilbert, Matthew Bradley, Louise Pike, Adiya Urazbayeva, Nur Haslina Ahmad Hanif, Yau Ke Ying, Alice Coleclough, Eilis Higgins, Lucy Morgan, Naomi Spencer, Tze Gee Ng, Sam Booth, Nilarnti Vignarajah, Tessa Chamberlain, Dongying Zhao, Nayanatara Nadeesha Tantirige, John Watts, Rebecca Walford, Amy Prideaux, Amelia Tee, Annabelle Hook, Adam Mounce, Emily Eccles, Ross Edwards, Kirtika Ramesh, Laura Bausor, Chania Lambrinudi, Angelica Sharma, Amy Handley, Alexandra Gordon, Lucy Allen, Rebecca Paddock, Harriet Penney, Lopa Banerjee, Lezia D'Souza, Kelly Thomas, Peter Havalda, Christopher Littler, Nathan West, Chris Subbe, Maria Hobrok, Richard Self, Vincent Hamlyn

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Journal of the American Medical Association* 2016; **315**: 801–10.

2. SepNet Critical Care Trials Group. Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study. *Intensive Care Medicine* 2016; **42**: 1980–9.

3. Vincent J-L, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. *Lancet Respiratory Medicine* 2014; **2**: 380–6.

4. Rohde JM, Odden AJ, Bonham C, Kuhn L, Malani PN, Chen LM, et al. The epidemiology of acute organ system dysfunction from severe sepsis outside of the intensive care unit. *Journal of Hospital Medicine* 2013; **8**: 243–7.

5. Angus DC, Seymour CW, Coopersmith CM, Deutschman CS, Klompas M, Levy MM, et al. A Framework for the Development and Interpretation of Different Sepsis Definitions and Clinical Criteria. *Critical Care Medicine* 2016; **44**: e113–21.

6. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; **101**: 1644–55.

7. Szakmany T, Lundin RM, Sharif B, Ellis G, Morgan P, Kopczynska M, et al. Sepsis Prevalence and Outcome on the General Wards and Emergency Departments in Wales: Results of a Multi-Centre, Observational, Point Prevalence Study. *PLoS ONE* 2016; **11**: e0167230.

8. Sharif B, Lundin RM, Morgan P, Hall JE, Dhadda A, Mann C, et al. Developing a digital data collection platform to measure the prevalence of sepsis in Wales. *Journal of the American Medical Informatics Association* 2016; **23**: 1185–9.

9. Shankar-Hari M, Deutschman CS, Singer M. Do we need a new definition of sepsis? *Intensive Care Medicine* 2015; **41**: 909–11.

10. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A,

et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Journal of the American Medical Association* 2016; **315**: 762–74.

11. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation* 2013; **84**: 465–70.

12. McGinley A, Pearse RM. A national early warning score for acutely ill patients. *British Medical Journal* 2012; **345**: e5310–0.

13. Arulkumaran N, Harrison DA, Brett SJ. Association between day and time of admission to critical care and acute hospital outcome for unplanned admissions to adult general critical care units: cohort study exploring the 'weekend effect'. *British Journal of Anaesthesia* 2017; **118**: 112–22.

14. Aldridge C, Bion J, Boyal A, Chen Y-F, Clancy M, Evans T, et al. Weekend specialist intensity and admission mortality in acute hospital trusts in England: a cross-sectional study. *Lancet* 2016; **388**: 178–86.

15. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Medicine* 1996; **22**: 707–10.

16. Pandharipande PP, Shintani AK, Hagerman HE, St Jacques PJ, Rice TW, Sanders NW, et al. Derivation and validation of Spo2/Fio2 ratio to impute for Pao2/Fio2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. *Critical Care Medicine* 2009; **37**: 1317–21.

17. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Aassociation Journal* 2005; **173**: 489–95.

18. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Medicine* 2003; **29**: 530–8.

19. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. *Journal of the American Medical Association* 2017; **317**: 290–300.

20. Freund Y, Lemachatti N, Krastinova E, Van Laer M, Claessens Y-E, Avondo A, et al. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the

Emergency Department. *Journal of the American Medical Association* 2017; **317**: 301–8.

21. Dorsett M, Kroll M, Smith CS, Asaro P, Liang SY, Moy HP. qSOFA Has Poor Sensitivity for Prehospital Identification of Severe Sepsis and Septic Shock. *Prehospital Emergency Care* 2017; **15**: 1–9.

22. Finkelsztein EJ, Jones DS, Ma KC, Pabón MA, Delgado T, Nakahira K, et al. Comparison of qSOFA and SIRS for predicting adverse outcomes of patients with suspicion of sepsis outside the intensive care unit. *Critical Care* 2017; **21**: 73.

23. Giamarellos-Bourboulis EJ, Tsaganos T, Tsangaris I, Lada M, Routsi C, Sinapidis D, et al. Validation of the new Sepsis-3 definitions: proposal for improvement in early risk identification. *Clinical Microbiology and Infection* 2017; **23**: 104–9.

24. Churpek MM, Snyder A, Han X, Sokol S, Pettit N, Howell MD, 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. *American Journal of Respiratory and Critical Care Medicine* 2017; **195**: 906–11.

25. Donnelly JP, Safford MM, Shapiro NI, Baddley JW, Wang HE. Application of the Third International Consensus Definitions for Sepsis (Sepsis-3) Classification: a retrospective population-based cohort study. *Lancet Infectious Diseases* 2017; doi: 10.1016/S1473-3099(17)30117-2 .

26. Besen BAMP, Romano TG, Nassar AP, Taniguchi LU, Azevedo LCP, Mendes PV, et al. Sepsis-3 definitions predict ICU mortality in a low-middle-income country. *Annals of Intensive Care* 2016; **6**: 107.

27. Hancock C. A national quality improvement initiative for reducing harm and death from sepsis in Wales. *Intensive and Critical Care Nursing* 2015; **31**: 100–5.

28. Corfield AR, Lees F, Zealley I, Houston G, Dickie S, Ward K, et al. Utility of a single early warning score in patients with sepsis in the emergency department. *Emergency Medicine Journal* 2014; **31**: 482–7.

29. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. *New England Journal of Medicine* 2015; **372**: 1301–11.

30. Szakmany T, Ellis G, Lundin RM, Pignatelli I, Sharif B, Joshi S, et al. Sepsis in Wales on the general wards: results of a feasibility pilot. *British Journal of Anaesthesia* 2015; **114**: 1000–1.

31. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine* 2001; **29**: 1303–10.

32. Keep JW, Messmer AS, Sladden R, Burrell N, Pinate R, Tunnicliff M, et al. National early warning score at Emergency Department triage may allow earlier identification of patients with severe sepsis and septic shock: a retrospective observational study. *Emergency Medicine Journal* 2016; **33**: 37–41.

Table 1. Baseline characteristics of the patients in the whole cohort and comparing the survivors to those who died within 30 days.

	All patients (n=380)	Patients who died (n=78)	Survivors (n=302)	p-value
Sex				
Men	180 (47%)	46 (59%)	134 (44%)	0.019
Women	200 (53%)	32 (41%)	168 (56%)	
Age, year	74 (22 [82])	77 (17 [78])	73 (22 [78])	0.001
Systolic blood pressure, mmHg	113 (37 [169])	113 (36 [163])	112 (37 [146])	0.192
Respiratory rate, breaths/minute	20 (4 [27])	20 (5 [19])	20 (4 [27])	0.157
Heart rate, beats/minute	94 (25 [180]	95 (24 [123])	93 (24 [180])	0.665
Glasgow Coma Scale <15	51 (13%)	21 (25%)	30 (10%)	0.036
Temperature, Celsius	36.6 (1.2 [5.4])	36.5 (1.3 [4.4])	36.8 (1.2 [5.3])	0.142
AVPU<Alert,	20 (5%)	10 (12%)	10 (3%)	0.009
Clinical signs of infection				
Cough	176 (46%)	42 (53%)	134 (44%)	0.485
Dysuria	39 (10%)	10 (13%)	29 (10%)	0.583
Abdominal pain	68 (18%)	17 (22%)	51 (17%)	0.443
Headache	20 (5%)	1 (1%)	19 (6%)	0.135
Other	162 (55%)	34 (44%)	128 (42%)	0.871
Laboratory results				
White blood cell count, cells/mL	11250 (6900 [56000])	11700 (8900 [43700])	11200 (6300 [56000])	0.304
Platelet count, 1000/mL	269 (161 [920])*	223 (230 [866])	274 (150 [920])	0.051
Creatinine, micromol/L	76 (47 [671])*	89 (73 [650])	75 (39 [588])	0.085
Bilirubin micromol/L	10 (10 [570])*	14 (21 [339])	10 (9 [570])	0.022
Lactate	1.5 (2.0	1.8 (2.0	1.5 (1.0	0.468

mmol/L	[7.4])*	[7.4])	[1.8])	
Clinical frailty score	5 (3 [8])	4 (3 [7])	6 (3 [8])	0.001
SIRS				
0	20 (5%)	4 (5%)	16 (5%)	0.402
1	116 (31%)	18 (23%)	98 (32%)	
2	127 (33%)	28 (36%)	99 (33%)	
3	92 (24%)	24 (31%)	68 (22%)	
4	25 (7%)	4 (5%)	21 (7%)	
qSOFA				
0	152 (40%)	27 (34%)	125 (41%)	0.042
1	177 (47%)	33 (42%)	144 (48%)	
2	43 (11%)	15 (19%)	29 (10%)	
3	7 (2%)	3 (4%)	4 (1%)	
SOFA	2 (3 [10])	4 (3 [10])	2 (2 [9])	<0.001
SOFA≥2				
No	108 (28%)	10 (13%)	98 (32%)	<0.001
Yes	272 (72%)	67 (86%)	205 (67%)	
NEWS	4 (3 [12])	5 (4 [12])	4 (3 [9])	0.017
NEWS≥6				
No	265 (70%)	46 (59%)	219 (73%)	0.027
Yes	115 (30%)	32 (41%)	83 (27%)	

Values are N (%) for categorical variables or median (IQR [range]) for continuous variables. * Data unavailable in 36.3% (serum bilirubin), 7.9% (serum creatinine), 6.3% (platelet count) and 66.3% (serum lactate) cases
AVPU: Alert/Verbal response/Response to pain/Unresponsive; SIRS: systemic inflammatory response syndrome; qSOFA: quick Sequential Organ Failure Assessment score; SOFA: Sequential Organ Failure Assessment score; NEWS: National Early Warning Score

Table 2. Diagnostic performances of different sepsis definitions and clinical tools for the prediction of mortality at 30 days

	SEPSIS-1	SEPSIS-3	qSOFA≥2	SEPSIS-1 severe sepsis	NEWS≥6
Sensitivity, % (95%CI)	68 (56-78)	86 (76-92)	22 (14-33)	92 (83-97)	41 (30-53)
Specificity, % (95%CI)	47 (41-53)	32 (27-38)	89 (85-92)	24 (19-29)	73 (67-77)
Positive predictive value, % (95%CI)	25 (19-31)	25 (20-30)	34 (22-49)	24 (19-29)	30 (26-35)
Negative predictive value, % (95%CI)	85 (78-90)	90 (82-95)	82 (77-85)	92 (83-97)	70 (65-74)
Positive likelihood ratio (95%CI)	1.28 (1.06-1.54)	1.27 (1.13-1.43)	1.99 (1.17-3.39)	1.21 (1.11-1.33)	1.49 (1.08-2.06)
Negative likelihood ratio (95%CI)	0.68 (0.49-0.95)	0.43 (0.25-0.76)	0.88 (0.78-0.99)	0.32 (0.15-0.71)	0.81 (0.67-0.98)

SEPSIS-1: 1992 definition of sepsis criteria as defined by Bone et al. (6); SEPSIS-3: Third International Consensus Definition of sepsis criteria (1); qSOFA: quick Sequential Organ Failure Assessment score; SEPSIS-1 severe sepsis:

sepsis with organ dysfunction as defined by Bone et al. (6); NEWS: National Early Warning Score

Figure legends

Fig 1. Organisational flowchart of the study

207 patients gave consent on the day, 66 patient representatives gave assent and 107 patients were entered following professional assent. 51 patients (46 patients and 5 patient representatives) refused participation and no data was collected.

Fig 2. Patients identified having sepsis using the SEPSIS-1 and SEPSIS-3 clinical criteria

SOFA: Sequential organ failure assessment score; SIRS: systemic inflammatory response syndrome criteria; qSOFA: quick Sequential organ failure assessment score; SEPSIS-1 is defined by SIRS≥2. SEPSIS-3 is defined by SOFA≥2 and/or qSOFA≥2. 44 patients did not fulfill either SEPSIS-1 or SEPSIS-3 criteria.

Fig 3. Distribution of SEPSIS-1 and SEPSIS-3 clinical criteria in patients who died within 30 days (n=78)

SOFA: Sequential organ failure assessment score; SIRS: systemic inflammatory response syndrome criteria; qSOFA: quick Sequential organ failure assessment score; SEPSIS-1 is defined by SIRS≥2. SEPSIS-3 is defined by SOFA≥2 and/or qSOFA≥2. One patient did not fulfill either SEPSIS-1 or SEPSIS-3 criteria.

Fig 4. Survival difference of patients with different definitions of sepsis

Not meeting any sepsis criteria (black solid line), SEPSIS-1 definition (yellow dotted line), SEPSIS-3 definition (blue dashed line), both SEPSIS-1 and SEPSIS-3 definition (red dashed line with dots), * p=0.015