Evaluation of relationship between DiPS, NEWS and SIRS and 21-day mortality: A prospective observational study

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Abstract

Background: Sepsis is common and preventable mortality for septic shock is potentially high. Effective tools to improve the recognition, management and risk-stratification of sepsis are needed. This study aimed to validate and compare current tools for detecting mortality in patients presenting to an emergency department (ED) with possible sepsis and septic shock in Cardiff.

Methods: This prospective observational study was conducted from 15th to 28th May 2017 in the ED of a tertiary university hospital in Cardiff, recruiting patients aged 18 years or older with sepsis. The inclusion criteria were adults with SIRS ≥ 2 plus infection. Patients underwent a full ED work up. The primary outcome was 21-day mortality. Other outcomes were Intensive Care Unit (ICU) admission and hospital length of stay (LoS).

Results: 5116 patients were evaluated of whom 128 (2.5%) consecutive patients had sepsis, and 8/128 (6.3%) had septic shock. The 21-day mortality for sepsis was 8/128 (6.3%) and for septic shock was 3/8 (37.5%). Septic shock diagnosis based on the Diagnostic Investigation and Prediction of Shock (DiPS) criteria had the strongest association with 21-day mortality (P-value 0.0038).

Discussion: The DiPS definition of Septic Shock was shown to capture more patients and to be a better predictor of mortality compared to the traditional SIRS definition. Larger prospective studies are needed for validation of the DiPS Septic Shock definition.

Abbreviations: AUC: Area Under Curve; COPD: Chronic Obstructive Pulmonary Disease; dBP: Diastolic Blood Pressure; DiPs: Diagnostic Investigation and Prediction of Shock; ED: Emergency Department; GCS: Glasgow Coma Score; ICU: Intensive Care Unit; IQR: Interquartile Range; LoS: Length Of Stay; MAP: Mean Arterial Pressure; NEWS: National Early Warning Score; NIV: Non-invasive Ventilation; qSOFA: quick-SOFA; ROC: Receiver Operating Characteristic curve; sBP: Systolic Blood Pressure; SIRS: Systemic Inflammatory Response Syndrome; SSI: Signs & Symptoms of infection; UK: United Kingdom

Introduction

The incidence of sepsis is increasing owing partly to the growing prevalence of chronic conditions in the aging population [1]. Septic shock is associated with high mortality. In the United Kingdom (UK), sepsis is estimated to be responsible for 8% of deaths, costing the NHS £2.5 billion [2].

Early identification and management are crucial in reducing mortality. The current gold-standard treatment for sepsis in the UK is completion of the Sepsis-Six bundle within an hour of recognition [3]. If completed timely, it is associated with superior patient outcomes, reduced length of stay (LoS) and reduced mortality [4,5]. Currently however there are several pitfalls in the recognition and management of sepsis. Its presentation is heterogeneous and may by subtle, and failure to recognise and respond to sepsis has been regularly reported. Furthermore, in 2011, a Quality Systems Assessment reported that 34%

of clinical units did not have protocols for managing sepsis [4]. Necessary improvements have been highlighted as a national priority [5-7].

Although sepsis and septic shock are defined conceptually, producing an effective quantitative definition is not so straightforward [8]. Given the scarce supporting evidence for alternatives, definitions have remained largely unchanged for over two decades [7]. The traditional definition for sepsis, proposed in 1991, uses the host inflammatory response syndrome criteria (SIRS). This model risk stratifies patients into three categories: sepsis, severe sepsis and septic shock [7]. Limitations with this model are recognized. Furthermore, emerging insights into its pathophysiology have prompted a review of diagnostic criterion [8] Alternative tools have been suggested in the literature, differing predominantly by the cut-off values chosen.

The National Early Warning Score (NEWS) was developed based on the rationale that adverse events, such as cardiac arrests or

admissions to high dependency unit, are commonly preceded by deranged physiological parameters [9]. NEWS scoring provides an appropriate framework for risk-stratification, and when coupled with early intervention, can help prevent deterioration of patients [10]. In the context of sepsis it facilitates early recognition and appropriate escalation [11].

A recently introduced method for evaluating patients with possible sepsis outside the Intensive Care Unit (ICU) is quick-sOFA (qSOFA). A meta-analysis found that qSOFA was marginally superior to SIRS for predicting in-hospital mortality, but was inferior for sepsis diagnosis due to its poorer sensitivity [12].

A new tool for classifying emergency department (ED) shock, the Diagnostic Investigation and Prediction of Shock (DiPS) tool, was validated in patients presenting to an ED in Hong Kong [13]. It did not focus exclusively on patients with possible sepsis and did not compare common risk-stratification tools. However, given its more encompassing definition, compared to SIRS septic shock, it has the potential for greater sensitivity.

This study aimed to validate and compare current tools for detecting mortality in patients presenting to an ED with sepsis or septic shock in Cardiff. These included the traditional SIRs scoring system, NEWS and the DiPs Septic Shock definition.

Methods

In this prospective quality improvement project, the need for ethical approval and consent for quality improvement projects is not required in Cardiff University and Cardiff and Vale University Health Board Clinical R&D Departments.

Inclusion and Exclusion Criteria

Adult patients aged ≥18 years, attending any area in the ED, with SIRS ≥ 2 and infection were included. Patients with trauma, pregnancy, or who did not have a SIRS evaluation because of a minor injury were not included.

Definitions

An online database facilitated collection of a minimum dataset for each patient. Demographic data included postcode, age, sex, comorbidity and premorbid status. Clinical data included respiratory rate, heart rate, blood pressure, oxygen saturation, temperature and AVPU status. These measurements were used to calculate NEWS. Glasgow Coma Score was also recorded. Patients underwent a full ED work up. Investigations included full blood count, serum creatinine, urea and electrolytes, blood gases, blood glucose, clotting screen, International Normalised Ratio, liver function tests, blood culture, chest-X-ray and electrocardiogram. Therapeutic management details included time of initial antibiotic treatment, choice of antibiotic, volume of fluid resuscitation in the first six hours, use of noradrenaline and use of steroids. Date and time of presentation, time of triage, time first seen by a doctor and time transferred out of ED, triage category (Appendix) and the area in which the patient was predominantly managed were also recorded. Sepsis-Six compliance was assessed, including use of the Sepsis-Six form, documented measurement of urine output and lactate, administration of antibiotics within one hour, administration of intravenous fluids and oxygen, and taking blood cultures.

Patients were classified as having 'sepsis' if any two of the following Signs & Symptoms of infection (SSI) criteria were present alongside presumed or proven infection, namely temperature <36 or >38C; heart rate >90 bpm; white cell count >12 or <4x109/L; respiratory rate ≥ 20/ min; acutely altered mental state; and hypoglycaemia in the absence of diabetes [14].

Patients were classified as 'SIRS septic shock' if both of the following were present alongside presumed or proven infection: evidence of an 'abnormal' blood pressure defined as either a SBP <90 mmHg or a mean arterial pressure (MAP) <65 mmHg; and evidence of grossly abnormal acid-base status defined as a lactate level ≥ 4.0 mmol/L [14].

Patients were classified as 'DiPS septic shock' if any one of the following were present alongside presumed or proven infection: evidence of an 'abnormal' blood pressure defined as either a SBP <90 mmHg or a MAP <65 mmHg; or evidence of grossly abnormal acid-base status defined as a lactate level ≥ 4.0 mmol/L, or a base deficit of ≤ -5 mEq/L, or a pH ≤ 7.1 [13].

The primary outcome was 21-day mortality. Secondary outcomes were ICU admission, ICU LoS and hospital LoS.

Statistical Analysis

The data was analysed using MedCalc version 15.8 (MedCalc Software, Mariakerke, bvba, Belgium) and Microsoft Excel (Microsoft® Excel® for Mac 2011 version 14.7.2, Microsoft Corporation, Santa Rosa, California, USA) to calculate medians, means, standard deviations, interquartile ranges and confidence intervals. Chi squared and Fisher tests were also used. A P ≤ 0.05 was considered to be significant.

Results

Between 15th and 28th May 2017, 5116 patients attended the ED of whom 128 (2.5%) cases were recruited. Figure 1 illustrates the case selection process and flow of patients with sepsis through the ED. The incidence of sepsis was 25 per 1000 patient attendances. Eight of the 128 (6.3%) septic patients were classified as having septic shock based on the SIRS criteria, whilst 47 (36.7%) had septic shock based on DiPS criteria. The incidence of SIRS septic shock was 1.6 per 1000 patient attendances. The majority (n=87, 68.0%) was admitted to the wards. Four patients (3.1%) were admitted to ICU. The 21-day mortality rate for sepsis was 6.3% (8/128) and for septic shock was 37.5% (3/8). The average hospital LoS was 8.1 days ± 10.7 days.

Baseline Data

Table 1 shows the baseline characteristics of the study patients, whilst Table 2 shows their baseline investigations. The majority of patients were elderly and had significant comorbidities but lived independently. Twenty-nine percent of cases came from deprived areas in Wales. In the majority of patients, the NEWS showed deterioration from when they first presented.

NEWS, SIRS score, SIRS septic shock definition and DiPS septic shock definition as predictors of mortality

As shown in Table 3, 47 cases (36.7%) were classified to have Septic Shock based on DiPS definition. DiPS showed the strongest correlation with 21-day mortality, with an odds ratio of 14.0 (P-value 0.0151). This was closely followed by the more selective SIRS Septic Shock definition, which only included 8 septic shock cases (3.7%). Five of these patients died by day-21 (odds ratio 13.8, P-value 0.0023). Cases were also grouped based on a NEWS ≥ 7 and SIRs ≥ 3. The odds of death by day-21 in these groups were 7.2 (P-value 0.068) and 1.4 (P-value 0.414) respectively.

The association between each parameter of DiPS septic shock and 21-day mortality are shown in Table 4. A lactate ≥ 4.0mmol/L had the strongest association with 21-day mortality (P-value <0.0001), followed by base deficit (P-value 0.002) and sBP (P-value 0.012).

Table 1. Baseline Characteristics (N=128)

Variable	Numbers	
Age –years –Median (IQR)	65 (41.8 – 78.0)	
Male sex – no. (%)	68 (53)	
Index of deprivation – % – Median (IQR)[*1]	29 (9.0 – 73.1)	
Past medical history/ comorbidity – no. (%)	112 (87.5)	
Chronic Obstructive Lung Disease – no. (%)	30 (23.4)	
Hypertension – no. (%)	29 (22.7)	
Diabetes Mellitus – no. (%)	25 (19.5)	
Other chronic lung disease – no. (%)	20 (15.6)	
Malignancy – no. (%)	18 (14.1)	
Ischemic heart disease – no. (%)	15 (11.7)	
Heart failure – no. (%)	10 (7.8)	
Hyperlipidaemia – no. (%)	6 (4.7)	
Chronic Kidney Disease – no. (%)	5 (3.9)	
Premorbid status		
Independent – no. (%)	86 (67.2)	
Partially dependent – no. (%)	24 (18.8)	
Fully dependent – no. (%)	18 (14.1)	
Medication		
Proton pump inhibitor – no. (%)	41 (32.0)	
Antihypertensive – no. (%)	41 (32.0)	
Statin – no. (%)	35 (27.3)	
Antidepressant – no. (%)	31 (24.2)	
Oral hypoglycaemic agent – no. (%)	21 (16.4)	
Immunosuppressant (including steroids) – no. (%)	16 (12.5)	
Insulin – no. (%)	2 (1.6)	
SIRS Score on Admission		
0 – no. (%)	0 (0)	
1 – no. (%)	0 (0)	
2 – no. (%)	73 (57.0)	
3 – no. (%)	40 (31.3)	
4 – no. (%)	15 (11.7)	
Observations	First	Worst
Systolic Blood Pressure (sBP) – mmHg – Median (IQR)	126 (105.8 – 139.0)	107 (92.0 – 128.0)
Diastolic Blood Pressure (dBP) – mmHg – Median (IQR)	74 (59.0 – 82.0)	63 (51.0 – 76.0)
Mean Arterial Pressure (MAP) – mmHg – Median (IQR)	90 (77.5 – 100.6)	76 (64.3 – 93.3)
Pulse Pressure – mmHg – Median (IQR)	49 (39.0 – 62.0)	42 (34.8 – 56.3)
Heart Rate – bmp – Median (IQR)	105 (94.0 – 119.0)	99 (87.8 – 112.8)
Respiratory rate – bmp – Median (IQR)	22 (21.5-24.0)	20 (18.0 – 24.0)
Temperature – ºC – Median (IQR)	37.6 (37.0-38.5)	37.4 (36.6 – 38.2)
Oxygen Saturations (SaO$_2$) – Median (IQR)	96 (93.0 – 98.0)	97 (95.0 – 98.0)
FiO$_2$ – % - Median (IQR)	21 (21.0 – 21.0)	21 (21.0 – 28.0)
Glasgow Coma Score – Median (IQR)	15 (15.0 – 15.0)	15 (15.0 – 15.0)
NEWS	**First**	**Worst**
0 – no. (%)	0 (0)	0 (0)
1-3 – no. (%)	41 (32.0)	2 (1.6)
4-6 – no. (%)	51 (39.8)	60 (46.9)
7-9 – no. (%)	26 (20.3)	41 (32.0)
10-12 – no. (%)	7 (5.5)	19 (14.8)
13-18 – no. (%)	3 (2.3)	6 (4.7)
Triage Category		
1 – no. (%)	33 (25.8)	
2 – no. (%)	43 (33.6)	

3 – no. (%)	29 (22.7)
4 – no. (%)	23 (18.0)
Source of Infection	
Respiratory – no. (%)	61 (47.7)
Urinary tract – no. (%)	27 (21.1)
Abdomen – no. (%)	19 (14.8)
Skin/joint – no. (%)	13 (10.2)
Other*2 – no. (%)	7 (5.5)
Unknown – no. (%)	6 (4.7)
Acquired From	
Community	121 (94.5)
Nosocomial*3	7 (5.5)
*1calculated using Welsh Index of Multiple Deprivation (WIMD) 2014, 10% indicates the local area is in the '10% most deprived areas in Wales' [15]. *2tonsillitis, Pelvic Inflammatory Disease (PID), sinusitis *3recent discharge within 72 h.	

Table 2. Baseline Investigations (N=128)

Variable	Numbers
Electrocardiogram (N=108)	
Sinus rhythm – no. (%)	87 (80.5%)
Atrial fibrillation – no. (%)	17 (15.7%)
Ventricular rate – Median (IQR)	100 (99 – 114)
Blood Tests	
Haemoglobin – g/dL – Median (IQR)	133.0 (117.0 – 146.0)
White Cell Count - /L – Median (IQR)	13.0 (9.5 – 15.0)
Platelet - /L – Median (IQR)	236 (184.0 – 306.0)
Neutrophils - /L – Median (IQR)	10.0 (6.73 – 12.0)
Lymphocytes - /L – Median (IQR)	1.05 (0.60 – 1.70)
Haematocrit – g/dL – Median (IQR)	0.40 (0.36 – 0.43)
Creatinine – μmol/L – Median (IQR)	76.0 (67.0 – 103.5)
Baseline creatinine* – μmol/L – Median (IQR)	71.0 (59.5– 83.5)
Urea – mmol/L – Median (IQR)	4.9 (3.9 – 7.4)
Sodium – mmol/L – Median (IQR)	138.0 (135.5 – 140.0)
Potassium – mmol/L – Median (IQR)	4.10 (3.78 – 4.30)
Serum Glucose – mmol/L – Median (IQR)	6.9 (6.3 – 9.1)
Bilirubin - μmol/L – Median (IQR)	10.0 (7.0 – 16.0)
Alanine Transaminase – IU/l – Median (IQR)	21.0 (14.0 – 35.0)
Serum Albumin – g/L – Median (IQR)	33.0 (29.0 – 36.0)
Prothrombin time – seconds – Median (IQR)	13.6 (12.5 – 15.1)
Partial Thromboplastin Time (PTT) - seconds – Median (IQR)	29.8 (27.4 – 33.7)
C-Reactive Protein – mg/L – Median (IQR)	60.0 (26.0 – 130.0)
Venous Blood Gas	
pH – Median (IQR)	7.42 (7.37 – 7.45)
Partial Pressure of Oxygen (PaO_2) – mmHg – Median (IQR)	5.64 (3.73 – 8.15)
Partial Pressure of Carbon Dioxide ($PaCO_2$) – mmHg – Median (IQR)	5.06 (4.5 – 6.0)
Base deficit – mmol/ L – Median (IQR)	0.70 (-2.3 – 2.65)
Bicarbonate – mmol/L – Median (IQR)	24.20 (21.85 – 26.10)
Lactate – mmol/L – Median (IQR)	1.60 (0.95 – 2.75)
*pre-admission baseline creatinine	

Table 3. Comparing SIRS and DiPS Septic Shock Definitions and NEWS and SIRS scores as predictors of 21-day mortality

		21-Day Mortality – no.		Odds Ratio (95% CI)	Sx(1%)	Sp (1%)	P-value
		Survived (N=120)	Died (N=8)				
DiPS Septic Shock	Yes	40	7	14.0 (1.7-117.7)	88	67	0.0151*
	No	80	1				
SIRS Septic Shock	Yes	5	3	13.8 (2.5 – 74.7)	38	96	0.0023*
	No	115	5				
NEWS>6	Yes	59	7	7.2 (0.9 – 60.6)	88	51	0.0680
	No	61	1				
SIRS>2	Yes	51	4	1.4 (0.3 – 5.7)	50	58	0.414
	No	69	4				

*results are statistically significant (P-value<0.05)
Sx – sensitivity
Sp – specificity

Table 4. DiPS Septic Shock parameters as predictors of 21-day mortality

DiPS Septic Shock Parameters		21-Day Mortality		Sx** (%)	Sp** (%)	P-value
		Survived (N=120)	Died (N=8)			
sBP (mmHg)	<90	25	6	19	98	0.012*
	>90	95	2			
MAP (mmHg)	<65	29	4	12	96	0.102
	>65	91	4			
Lactate (mmol/L)	≥ 4.0	8	5	63	93	<0.0001*
	1.5 - <4.0	74	2			
	<1.5	38	1			
pH	≤ 7.1	1	0	0	99	0.841
	7.1 – 7.3	4	0			
	>7.3	115	8			
Base deficit (mEq/L)	≤ -5	6	3	38	95	0.002*

*results are statistically significant (P-value<0.05)
Sx – sensitivity
Sp – specificity
** Where there are three groups, the lower two have been combined to form the reference group
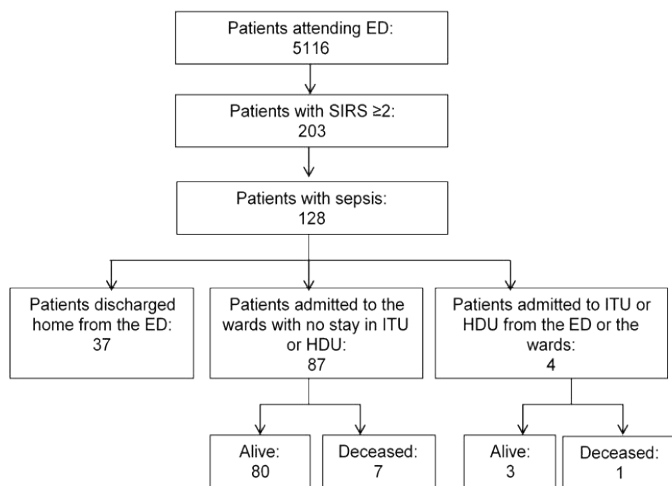

Figure 1. Flow of septic patients through the ED at University Hospital of Wales
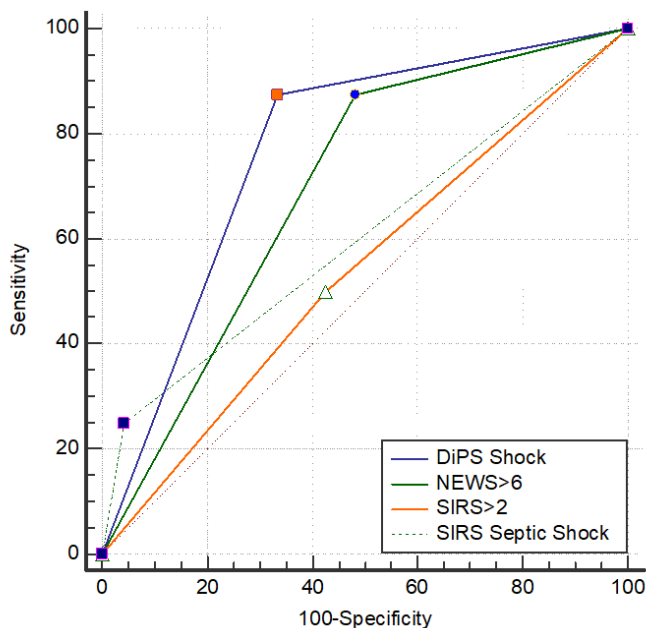

Figure 2. Receiver Operating Characteristic curve for NEWS and SIRS scores and SIRs and DiPS Septic Shock definitions

The validity of the four definitions are shown graphically in Figure 2. DiPS septic shock definition generated the greatest area under the Receiver Operating Characteristic curve (ROC) (AUC 0.771), followed by NEWS ≥ 7 (AUC 0.696), then SIRS septic shock (AUC 0.604) and lastly SIRS ≥ 3 (AUC 0.534). These values were not statistically significant, however the apparent trend is consistent with the statistically significant results shown in Table 2.

Discussion

This prospective study confirms that in a heterogenous group of 5116 ED attendees, sepsis is a relatively common condition with septic shock being associated with high mortality and morbidity. The incidence of sepsis was 25 per 1000 patient attendances and the incidence of SIRS septic shock was 1.6 per 1000 patient attendances.

The demographic and clinical features of the study patients are consistent with the literature. In accordance with the already known high risk groups [16], the study cohort had a median age of 65 (41.8–78.0), with 14% (n=18) being fully dependent, 87.5% (n=112) having a comorbidity and 12.5% (n=16) being on an immunosuppressant. Kang, et al. (2011) showed that pulmonary disease, malignancy and liver disease were the strongest risk factors for septic shock, and strong predictors of mortality [17]. Pulmonary disease was the most common comorbidity in our study (39%, Table 1), with Chronic Obstructive Pulmonary Disease (COPD) accounting for the majority [17]. Consistent with previous studies, respiratory tract infections were the most common site of infection [18].

Previous guidelines used SIRS to define sepsis and septic shock. The theories behind these definitions have been criticized as out-of-date and irrelevant. However a recent meta-analysis suggests the proposed replacement–qSOFA–may add little advantage in prognosis and none in detection [12]. Therefore, our study evaluated NEWS and DiPS as potential alternatives.

DiPS septic shock and all its individual parameters, except pH and MAP, correlated with 21-day mortality. MAP has been well reported to be independently associated with ICU admission and hospital mortality for patients with Septic Shock [19]. The lack of association in this study may be due to inadequate sample size. The prognostic role of low pH is unclear in the literature. For example, Goodhart, et al. (2015) found that low pH was associated with higher mortality in patients with pneumonia treated with non-invasive ventilation (NIV) but not in patients with COPD treated with NIV [20]. Further studies are needed to define the relevance of pH as a prognostic indicator.

The SIRS septic shock definition captures a subset of patients defined under the DiPS septic shock definition. This subset was also associated with poorer prognosis. DiPS Septic Shock definition generated the greatest area under the ROC curve suggesting it had a superior combination of sensitivity and specificity. Although this result was not statistically significant, it highlights the need to re-evaluate the current definitions of Septic Shock that is advocated in the guidelines.

NEWS is known to be a strong predictor of mortality. It has been adopted as a generic screening and assessment risk-stratification tool throughout the UK [21]. Correspondingly in this study, NEWS ≥ 7 was significantly associated with worse 21-day mortality. SIRS score ≥ 3 was not shown to be associated with worse 21-day mortality (P-value 0.35). There are several plausible reasons explaining why NEWS is superior in predicting mortality. The greater number of variables monitored facilitates the detection of a physiological abnormality [9]. The SIRS sepsis criterion does not include blood pressure and lactate, both of which are valuable risk-stratification tools [22]. Furthermore the type of scoring system may have an influence on its sensitivity. NEWS scoring produces a continuum from 0-20, whereas SIRS scoring is discrete, for which patients score 1 or 0 for each parameter based on whether the cut-off value is met. NEWS thus allows inferences to be made from the cumulative effect of deranged parameters even if they are below the specific cut-off value specified in the SIRS criteria. On the other hand, concerns have been expressed about NEWS because of its high sensitivity and exclusion of some parameters such as urine output [9].

Given the complexity and heterogeneity of sepsis, there may be no perfect scoring system for all situations, and experienced clinical judgement, although also not perfect [23], should be considered. Nevertheless there is a clear need to optimize our current definitions, to improve early recognition and appropriate management.

This study has a number of limitations. This was a preliminary, although painstakingly detailed analysis of consecutive cases, and the sample size was small. This compromised our ability to perform multivariate analysis. Nevertheless it was sufficient to generate some statistically significant results. Secondly this was a single centre study, potentially limiting its generalizability. Thirdly, we have not included qSOFA in our comparisons. This is partly because qSOFA was not developed on real-world data, and subsequent studies have suggested that it offers little for front-door assessment.

Conclusion

Septic shock is associated with a high 21-day mortality. The DiPS definition of Septic Shock was shown to capture more patients and to be a better predictor of mortality compared to the traditional SIRS definition. Larger prospective studies are needed for validation of the DiPS Septic Shock definition.

Acknowledgements

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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