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Title

Febrile children in the Emergency Department: frequency and predictors of poor outcome.

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Running Title

Outcome in febrile children.

Abstract

Aim: To evaluate the frequency and predictors of poor outcome in febrile children presenting to the Emergency Department.

Methods: Retrospective observational study from the Emergency Department of The Royal Children's Hospital, Melbourne, Australia. All children with presenting complaint of fever or triage temperature $>38^{\circ}\text{C}$ over a 6-month period were included. Poor outcome was defined

as: new organ dysfunction or the requirement for organ support therapy (inotrope infusion, mechanical ventilation, renal replacement therapy, extra-corporeal life support). Predictors evaluated were: initial vital signs, blood tests, and clinical scores. Odds ratio, sensitivity, specificity, and area under the receiver-operating characteristics curve was calculated for each predictor variable.

Results: Between Jan-June 2019, 6217 children met inclusion criteria. Twenty seven (0.4%) developed new organ dysfunction, 10 (0.2%) required organ support therapy (inotrope infusion in 5, mechanical ventilation in 6, renal replacement therapy in 1, extra-corporeal life support in 1). Odds of new organ dysfunction, requirement for inotropic support and mechanical ventilation were higher with abnormal initial vital signs, blood tests, and clinical scores, though overall test characteristics were poor due to infrequency.

Conclusion: Poor outcomes were uncommon among febrile children presenting to the Emergency Department. Vital signs, blood tests, and clinical scores were poor predictors.

Keywords:

Fever, child, multiple organ failure, emergency service hospital, critical care

Key Notes

Fever is a common reason for children to seek medical attention, yet differentiating mild self-limited illness from severe life-threatening illness can be difficult early in the disease course.

In a large group of children presenting to a tertiary paediatric Emergency Department with febrile illness, we found that poor outcomes were rare.

Predicting which febrile children were at risk of poor outcome was difficult due to infrequency.

Introduction

Early identification of febrile children who are at risk of poor outcomes is important. Early initiation of appropriate therapy may alter the clinical course of disease and reduce the risk of deterioration and death.(1) *It may also facilitate* appropriate resource allocation, including location of care, invasiveness and frequency of monitoring, ongoing investigations and treatment, and targeted follow-up. Predictors of poor outcome *may be applied clinically* for early risk stratification, allowing comparison between similar patient groups, benchmarking of care, and reducing bias in quality improvement initiatives.(2) Lastly, early identification of febrile children at risk of poor outcomes *may have research applications* for studying early resuscitative therapies through enrollment in clinical trials.

Vital signs are routinely evaluated to identify children with life-threatening infections during initial medical assessment or triage. Abnormalities in multiple vital signs or extreme derangements in single vital signs are used as triggers for more rapid medical review and early initiation of care. However, thresholds for abnormal vital signs have been determined by expert consensus, and not validated as indicators of severity of disease or predictors of poor outcome.(3) Abnormalities in vital signs may represent a normal adaptive physiological response to infection.(4) Hypotension, a defining feature of shock, is thought to be a late sign indicative of severe disease, yet no clear definition for hypotension in children exists.(5)

Blood tests that have been proposed as predictors of poor outcome in children with fever include venous lactate, serum creatinine, white cell count, platelet count, and international normalized ratio (INR). Venous lactate is commonly measured in the ED as part of blood gas analysis for children suspected of having life-threatening infections. Elevated serum lactate may be associated with poor outcome.(6) Infection-induced acute kidney injury (AKI), manifest as elevated serum creatinine, is thought to be relatively common in children with severe infections, and as an early marker of organ dysfunction may predict poor outcome.(7) Low white cell and platelet counts have been validated in children in the Intensive Care Unit (ICU) as predictors of mortality, while coagulopathy, as indicated by an elevated INR, may also be a poor prognostic marker.(8, 9)

Clinical scores that have been proposed as predictors of poor outcome in febrile children include the Systemic Inflammatory Response Syndrome (SIRS) criteria, the Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score, the quick Sequential Organ Failure

Assessment score (qSOFA), and the quick PELOD-2 score (qPELOD-2) (Figure 1)(3, 8, 10, 11). *The predictive performance of these in scores for poor outcome in undifferentiated febrile children in the ED is unknown.*

The aim of this study was to determine the frequency of poor outcome in undifferentiated children with fever in the ED, and evaluate predictors of poor outcome using variables available early during patient management. We defined poor outcome as the development of new organ dysfunction and the requirement for organ support therapy, and included initial vital signs, initial blood tests, and clinical scores as predictor variables.

Patients and Methods

Study Design

The study was designed as a retrospective cohort study, and approved by the hospital institutional review board (The Royal Children's Hospital Human Research and Ethics Committee (HREC), approval QA/54985/RCHM-2019). Methodology and reporting of results followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.(12)

Study Setting and Population

The study setting was the ED of The Royal Children's Hospital, Melbourne, Australia, a tertiary children's hospital with an annual ED census of >90 000 children.

All patients with 'fever' in their triage description or an initial triage temperature of $>38.0^{\circ}\text{C}$ were included. This patient group was chosen to include the population in whom predictors of poor outcome might be applied. Patients of all ages were included, there were no exclusion criteria.

The primary outcome was the frequency of new organ dysfunction and requirement for organ support therapy in the study population. We evaluated vital signs (heart rate, respiratory rate, blood pressure, and Glasgow Coma Scale (GCS) score), bloods tests (venous lactate, creatinine, white cell count, platelet count, and INR), and clinical scores (SIRS, qSOFA, and qPELOD-2) as predictor variables.

We extracted demographic data, initial vital signs, blood test results, diagnosis, disposition, organ support therapies, daily organ dysfunction scores for patients admitted to PICU, and mortality. *Daily organ dysfunction scores were used for the assessment of new organ dysfunction.* Patients who survived and were not admitted to or were discharged from PICU were assumed to have no organ dysfunction.(8) Patients who did not have blood tests performed and who survived were assumed to have normal values. *Missing vital signs were assumed to be normal. All study data were extracted from the electronic medical record through an automated process. Study related data, including vital signs and blood tests, were automatically entered into the Electronic Medical Record during routine patient care.* One hundred electronic medical records were randomly selected and manually checked for accuracy of extracted data.

Definitions

Organ dysfunction was defined according to PELOD-2 criteria.(8) New organ dysfunction was defined as organ dysfunction that was not present on initial assessment or initial blood tests. Organ support therapy was defined as: inotrope infusion, mechanical ventilation, renal replacement therapy (RRT), or extracorporeal life support (ECLS).

Initial temperature and vital signs were defined as those taken at triage or on initial assessment. Initial blood tests were defined as the first blood test obtained, time limited to within 3 hours of initial ED presentation.

Abnormal vital signs for age were defined according to SIRS criteria (for heart rate, respiratory rate, and systolic blood pressure (SBP)), qSOFA criteria (for respiratory rate, GCS score, and SBP), and qPELOD-2 criteria (for heart rate, systolic and mean blood pressure (MBP), and GCS score).(3, 11, 13)

Abnormal blood test results for age were defined according to PELOD-2 criteria (for creatinine, platelet count, and white cell count), lactate according to validated thresholds (≥ 2 and ≥ 4 mmol/L), and INR according to Sepsis-Induced Coagulopathy criteria.(6, 8, 14)

Statistical Analysis

Descriptive statistics were reported with median and interquartile range (IQR) for continuous variables and frequency with percentage for categorical variables. Association between initial vital signs, blood tests, clinical scores and the development of new organ dysfunction and requirement for organ support therapy were reported as odds ratios (OR) with 95% confidence intervals (CI). The discriminative ability of predictor variables was measured using the area under the receiver-operating characteristics curve (AUROC), with sensitivity and specificity calculated for each variable. Statistical analysis was performed using Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Results

Over the 6-month study period, 6217 children presented to the ED with a febrile illness out of 45051 overall presentations (13.8%). *Demographic, disposition, and outcome data were extracted for all presentations meeting inclusion criteria. Temperature, heart rate, and respiratory rate were recorded in >95% of presentations. Blood pressure was recorded in 3776 (60.7%), and 584 (9.4%) had a formal GCS score recorded (the remainder were scored as 'alert'). Serum lactate was evaluated in 499 (8.0%) presentations, blood count values evaluated in 1439 (23.1%), and coagulation values in 110 (1.8%). There were no lost data, and manual review of medical records correlated with electronically extracted study data.* Four thousand and sixty three (65.4%) presentations were discharged home, 2154 (34.6%) were admitted to hospital, and 32 (0.5%) were admitted to PICU (Table 1). Three thousand six hundred and twenty seven (58.3%) were children <3 years of age (Figure 2). The most frequent ED diagnoses were acute febrile illness (2608; 42.0%) and upper respiratory tract infection (1490; 24.0%).

New organ dysfunction developed in 27 patients (0.4%), of whom 10 required organ support therapy (0.2%: inotropic support in 5, mechanical ventilation in 6, RRT in 1, and ECLS in 1). One patient required all of: inotropic support, mechanical ventilation, RRT, and ECLS. One patient with complex congenital cardiac disease died without receiving organ support therapy and was included in the analysis. *Five patients were admitted to PICU who did not develop new organ dysfunction or require organ support therapy: 2 with croup who had required multiple adrenaline nebulas prior to PICU admission, and 3 patients on ventricular assist device who were admitted to PICU for observation only.*

The test characteristics of vital signs, blood tests, and clinical scores for predicting the development of new organ dysfunction and the requirement for organ support therapy (inotropic support and mechanical ventilation) are shown in Tables 2 and 3. Test characteristics for predicting RRT and ECLS were not calculated due to the infrequency of these outcomes. The best performing ED predictors of new organ dysfunction included: GCS<11, INR $\geq$ 1.2, lactate $\geq$ 4.0mmol/L, and qPELOD-2 (SBP) score $\geq$ 1. The best performing predictors of the requirement for inotropic support included: initial hypotension (using PELOD (SBP)), lactate $\geq$ 4mmol/L, INR $\geq$ 1.2, and qPELOD (SBP) score $\geq$ 1. The best predictors of the requirement for mechanical ventilation included: GCS <11, lactate $\geq$ 4mmol/L, INR $\geq$ 1.2, and qSOFA=3. All predictor variables had poor test characteristics for the development of new organ dysfunction and the requirement for organ support therapy in this patient population.

Discussion

In this study set in a large tertiary ED in a metropolitan area of a high-income country, very few children presenting to the ED with febrile illness developed new organ dysfunction or required organ support therapy. Overall, 27/6217 (0.4%) children developed new organ dysfunction, and 10/6217 (0.2%) required organ support therapy. This is in keeping with the low prevalence of poor outcomes in other ED-based studies in high-income countries in the post pneumococcal and meningococcal vaccination era.(15) The rarity of poor outcomes in the undifferentiated population of febrile children presenting to the ED has several implications. For clinicians and parents, it is re-assuring that the majority do not develop new organ dysfunction or require organ support therapy. Despite the infrequency of poor outcome in this patient group, the overall admission rate for children with febrile illness was high (2154/6217, 34.6%), as was the PICU admission rate for children who did not require organ support therapy (22/32; 68.8%). Febrile children may have been admitted to hospital for other therapies, such as antibiotics, nutritional support, or supplemental oxygen therapy, or in the presence of significant co-morbidities (such as fever and neutropenia). In addition, the known difficulties differentiating self-limited from life-threatening infections early in their course, and / or the clinical utility of close observation and monitoring for early signs of deterioration may have contributed to the clinical decision for hospital admission. For researchers, the finding that poor outcomes in febrile children were rare limits their feasibility as outcome measures for clinical trials. Alternative outcomes that are clinically important and patient-

focussed may need to be developed for clinical trials in the high income setting, such as resource utilisation.

All predictor variables evaluated in this study for the development of new organ dysfunction or the requirement for organ support therapy had poor test characteristics and wide confidence intervals. This relates to the infrequency of these outcomes in the study population.

Vital signs: Heart rate and respiratory rate were often elevated in undifferentiated febrile children. This did not confer an increased risk for the development of organ dysfunction or the requirement for organ support therapy. Hypotension, based on systolic or mean blood pressure, was present in a small minority of children with febrile illness. Though hypotension is thought to be a late sign of acute circulatory failure in children, the majority in this study with initial hypotension did not subsequently require organ support therapy in the form of an inotrope infusion. This may have resulted from an adequate response to fluid bolus administration, though the evidence supporting its use for this purpose is limited.(16) The utility of systolic versus mean blood pressure values as predictor variables, and thresholds based on SIRS versus PELOD-2 values, require further evaluation in patient groups with a higher prevalence of poor outcomes. GCS score was abnormal (<11) in very few children. When abnormal, however, GCS score was a strong predictor of the requirement for mechanical ventilation. This observation has construct validity, in that decreased conscious state is often the *indication* for mechanical ventilation. Abnormal GCS score was, however, not predictive of the requirement for inotropic support. This may have resulted from abnormal GCS being secondary to seizures or central nervous system infection rather than due to cerebral hypoperfusion in the majority of cases.

Blood tests: Elevated venous lactate significantly increased the odds for the development of new organ dysfunction and the requirement for organ support therapy (both mechanical ventilation and inotropic support), with increased risk by higher lactate level. These findings are in keeping with prior ED studies, where elevated venous lactate has been associated with an increased relative risk of developing organ dysfunction within 24 hours, and higher venous lactate levels associated with higher risk of new organ dysfunction and death.(6) Elevated initial creatinine was associated with increased odds for the development of new organ dysfunction and the requirement for organ support therapy. Early detection of

infection-induced AKI, as evidenced by abnormally elevated serum creatinine, has been validated as an early predictor of mortality in the PICU population.(8) Elevated initial INR significantly increased the odds for the development of new organ dysfunction and the requirement for organ support therapy. This is consistent with current understanding of the pathophysiology of sepsis induced coagulopathy,(9) though INR is not included in the validated PELOD-2 score, despite being assessed in derivation studies.(8) This may be because the PELOD-2 score was validated as a predictive tool for mortality in undifferentiated PICU patients, not restricted to those with life-threatening infections, or because the effect of INR on outcome is already contained in other PELOD-2 criteria. Low initial platelet count was associated with increased odds for the development of new organ dysfunction and the subsequent requirement for organ support therapy. Low platelet count has been validated as a predictor of mortality in the PICU setting.(8) Low white cell count increased the odds for the development of new organ dysfunction and the subsequent requirement for inotropic support but not mechanical ventilation. Low white cell count not due to chemotherapy has been validated in the PICU setting as a predictor of death.(8)

Clinical scores: Clinical scores based on combinations of abnormal vital signs performed variably as predictors of the development of new organ dysfunction or the requirement for organ support therapy. Febrile children often met SIRS and qSOFA criteria due to elevated HR and RR, which were poor predictors of the development of new organ dysfunction or the requirement for organ support therapy. This is in keeping with validation studies for SIRS and qSOFA in the PICU setting, where SIRS and qSOFA <2 had AUROC of 0.63 and 0.78, respectively, for predicting hospital mortality.(11) The qPELOD-2 score, with its emphasis on haemodynamic derangements, had better performance in predicting the development of new organ dysfunction and the requirement for organ support therapy. This is in keeping with the excellent performance of the qPELOD-2 score in the PICU population with suspected infection for predicting hospital mortality.(17)

This study identifies some variables that may be used to develop a composite infection severity score for validation in a higher-risk patient group. Such clinical scores have been developed and validated in the PICU setting using some clinical and biochemical variables.(18) High-risk patient groups of children that may be used for validation of such clinical scores may be similar to those used for validation of the Sepsis-3 criteria: patients with suspected infection who had blood cultures taken and were admitted to hospital for the

administration of intravenous antibiotics.(19) Lastly, the inclusion of outcomes used in the validation of the Sepsis-3 criteria, such as ICU length-of-stay ≥ 3 days, may be important to include as poor outcomes in future validation studies in children.

Limitations

This was a retrospective, observational, single centre study using data extracted from an electronic medical record. As a single centre study, some important outcomes, such as PICU admission, may have been influenced by local policy and procedure rather than disease severity, and may not be generalisable to other hospitals or health services. Other patient and treatment factors may also have been hospital specific and not generalisable. EMR search allowed for a much larger data-set than could be obtained through manual record searching alone, but could not capture intangible information such as clinician gestalt or parental level of concern which may affect clinical decision making.(20) Despite this large sample size, poor outcomes were uncommon and resulted in wide confidence intervals in predictor variables. *Patients who did not have blood tests performed and who survived were assumed to have normal values. This may have been an incorrect assumption in some cases.* Organ dysfunction scores did not take into account concurrent organ support therapies, which may have resulted in artificial normalization of organ dysfunction parameters. Many predictor variables have been validated only in the PICU setting, their evaluation in the ED setting was exploratory. Due to lack of a validated risk adjustment tool, calculations were not adjusted. Biological coupling of organ dysfunction present on initial assessment and the development of new organ dysfunction may have been an uncontrolled confounder.

Conclusion

The development of new organ dysfunction and the requirement for organ support therapy is rare among febrile children presenting to the ED. Predicting poor outcome in this patient group using existing predictor variables is difficult. An infection severity score using combined clinical and biochemical variables may have better test characteristics, especially if applied to a higher risk patient group.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Table 1. Demographic data, vital signs, blood tests, clinical severity scores, and Emergency Department diagnoses for children presenting with febrile illness.

	All Patients (n=6217)	Discharged (n=4063)	Admitted: Total (n=2154)	Admitted: ED SSU (n=1076)	Admitted: Ward (n=1046)	Admitted: PICU (n=32)
Demographics						
Age, years; median (IQR)	2.4 (1.1 – 5.0)	2.4 (1.2 – 4.9)	2.2 (1.1 – 5.2)	2.0 (1.1 – 4.4)	2.3 (0.9 – 5.6)	4.1 (0.7 – 10.8)
Sex, male; n(%)	3411 (54.9)	2187 (53.8)	1224 (56.8)	612 (56.9)	612 (56.9)	13 (40.6)
Weight, kg; median (IQR)	13.6 (10.2 – 19.4)	14.0 (10.5 – 19.5)	13.0 (9.6 – 19.2)	12.5 (9.9 – 18.0)	13.0 (8.9 – 20.0)	15.5 (9.7 – 29.3)
Vital signs						
Temperature, °C; median (IQR)	38.1 (37.1 – 38.7)	38.1 (37.0 – 38.7)	38.2 (37.4 – 38.8)	38.3 (37.3 – 38.9)	38.2 (37.4 – 38.7)	38.3 (37.7 – 39.1)
HR, beats per minute; median (IQR)	140 (120 – 156)	135 (120 – 150)	144 (125 – 161)	141 (124 – 160)	148 (127 – 164)	155 (122 – 178)
Tachycardia (SIRS); n(%)	1377 (22.2)	708 (17.4)	669 (31.1)	274 (25.5)	378 (36.1)	17 (53.1)
Tachycardia (PELOD); n(%)	93 (1.5)	22 (0.5)	71 (3.3)	24 (2.2)	42 (4.0)	5 (15.6)
MBP, mmHg; median (IQR)	78 (71 to 86)	79 (72 – 86)	78 (70 – 86)	77 (70 – 86)	78 (71 – 87)	77 (73 – 92)
SBP, mmHg; median (IQR)	104 (96 to 112)	104 (96 to 112)	104 (95 to 113)	103 (95 to 112)	104 (95 to 113)	103 (93 to 113)
Hypotension (SBP, SIRS); n(%)	74 (1.2)	28 (6.9)	46 (2.1)	17 (1.6)	29 (2.8)	1 (3.1)

Hypotension (SBP, PELOD); n(%)	154 (2.5)	72 (1.8)	82 (3.8)	41 (3.8)	41 (3.9)	3 (9.4)
Hypotension (MBP); n(%)	165 (2.7)	72 (1.8)	93 (4.3)	46 (4.3)	45 (4.3)	2 (6.3)
RR, breaths per minute; median (IQR)	30 (26 to 38)	30 (26 – 36)	32 (26 – 42)	32 (26 – 40)	34 (28 – 44)	35 (24 – 49)
Tachypnoea (SIRS); n(%)	4726 (76.0)	2889 (71.1)	1837 (85.3)	842 (78.3)	964 (92.2)	31 (96.9)
GCS; median (IQR)	15 (15 – 15)	15 (15 – 15)	15 (15 – 15)	15 (15 – 15)	15 (15 – 15)	10 (5 – 15)
GCS <11; n(%)	18 (0.3)	2 (0.0)	16 (0.7)	2 (0.2)	10 (10)	4 (12.5)
Blood tests						
Lactate, mmol/L; median (IQR), n=499	1.5 (1.2 – 2.1)	1.35 (1.0 – 1.7)	1.5 (1.2 – 2.1)	1.5 (1.3 – 2.2)	1.5 (1.1 – 2.1)	1.5 (1.2 – 2.0)
Lactate ≥2mmol/L; n(%)	108 (1.7)	7 (0.2)	101 (4.7)	10 (1.0)	85 (8.1)	6 (19.0)
Lactate ≥4mmol/L; n(%)	11 (0.2)	1 (<0.1)	10 (0.5)	1 (0.1)	8 (0.8)	1 (3.1)
Creatinine; median (IQR), n=1179	28 (23 to 39)					
Elevated creatinine (PELOD); n(%)	123 (2.0)	9 (0.2)	114 (5.3)	15 (1.4)	91 (8.7)	8 (25)
INR; median (IQR), n=110	1.1 (0.9 to 1.3)					
INR ≥1.2; n(%)	57 (1.0)	2 (0.0)	55 (2.6)	3 (0.3)	42 (4.0)	10 (31.3)
Platelet count; median (IQR), n=1493	271 (196 to 373)	252 (195 to 339)	276 (196 to 378)	250 (189 to 335)	291 199 to 391)	241 (199 to 332)
Platelet count 77-141; n(%)	90 (1.4)	16 (0.4)	74 (3.4)	18 (1.7)	53 (5.4)	3 (9.4)
Platelet count ≤76; n(%)	61 (1.0)	5 (0.1)	56 (2.5)	4 (0.4)	50 (5.0)	2 (6.3)
White cell count; median (IQR), n=1493	9.3 (5.9 to 13.4)	7.6 (5.0 to 10.8)	9.7 (6.1 to 14)	8.6 (5.5 to 12.3)	10.1 (6.2 to 14.4)	10.5 (7.3 to 13.1)

White cell count ≤ 2 ; n(%)	76 (1.2)	8 (0.2)	68 (3.2)	4 (0.4)	62 (6.1)	2 (6.3)
Scores						
SIRS; n(%)	4733 (76.1)	2911 (71.6)	1822 (84.6)	857 (79.6)	934 (89.3)	31 (96.9)
qSOFA; n(%)						
qSOFA ≥ 1 ; n(%)	4677 (75.2)	2876 (70.8)	1801 (83.6)	839 (78.0)	931 (89.0)	31 (96.9)
qSOFA ≥ 2 ; n(%)	1357 (21.8)	686 (16.9)	671 (31.2)	259 (24.1)	395 (37.8)	17 (53.1)
qSOFA=3; n(%)	5 (0.1)	0 (0)	5 (0.2)	1 (0.1)	2 (0.2)	2 (6.3)
qPELOD						
qPELOD ≥ 1 ; n(%)	258 (4.1)	93 (2.2)	165 (7.7)	71 (6.6)	87 (8.3)	7 (21.9)
qPELOD ≥ 2 ; n(%)	4 (0.1)	1 (<0.1)	3 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)
qPELOD=3; n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ED diagnosis; n(%)						
Diagnosis; n(%)						
Abscess / soft tissue infection	55 (0.9)	26 (0.6)	29 (1.3)	24 (2.2)	5 (0.5)	0 (0.0)
Febrile illness	2608 (41.9)	2022 (49.8)	586 (27.2)	332 (30.9)	242 (23.1)	12 (37.5)
Gastrointestinal						
Surgical	49 (0.8)	4 (0.1)	45 (2.1)	28 (2.6)	17 (1.6)	0 (0.0)
Vomiting / diarrhoea	281 (4.5)	83 (2.0)	198 (9.2)	94 (8.7)	104 (9.9)	0 (0.0)
Other (incl pain)	135 (2.2)	93 (2.3)	42 (1.9)	35 (3.3)	7 (0.7)	0 (0.0)
Haematological / oncological						
Blood disorder	44 (0.7)	16 (0.4)	28 (1.3)	16 (1.5)	12 (1.1)	0 (0.0)
Fever and risk of neutropaenia	109 (1.8)	16 (0.4)	93 (4.3)	1 (0.1)	91 (8.7)	1 (3.1)

Other	15 (0.2)	13 (0.3)	2 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)
Neurological						
Meningoencephalitis	7 (0.1)	0 (0.0)	7 (0.3)	0 (0.0)	5 (0.5)	2 (6.3)
Seizure	135 (2.2)	41 (1.0)	94 (4.4)	59 (5.5)	34 (3.3)	1 (21.9)
Other	15 (0.2)	12 (0.3)	3 (0.1)	0 (0.0)	3 (0.3)	0 (0.0)
Respiratory						
Upper respiratory tract infection	1490 (24.0)	1003 (24.7)	487 (22.6)	321 (29.8)	166 (15.9)	2 (6.3)
Lower respiratory tract infection	667 (10.7)	459 (11.3)	208 (9.7)	21 (2.0)	180 (17.2)	7 (21.9)
Reactive airway disease	203 (3.3)	54 (1.3)	149 (6.9)	91 (8.5)	57 (5.4)	1 (3.1)
Sepsis	39 (0.6)	0 (0.0)	39 (1.8)	0 (0.0)	34 (3.3)	4 (12.5)
Toxidrome	11 (0.2)	2 (0.0)	9 (0.4)	0 (0.0)	8 (0.8)	1 (3.1)
Urinary tract infection	234 (3.8)	141 (3.5)	93 (4.3)	31 (2.9)	62 (5.9)	0 (0.0)
Other	45 (0.7)	4 (0.1)	41 (1.9)	23 (2.1)	17 (1.6)	1 (3.1)

IQR=interquartile range, SIRS=Systemic Inflammatory Response Syndrome, PELOD=Pediatric Logistic Organ Dysfunction Score, SBP=systolic blood pressure, MBP=mean blood pressure, RR=respiratory rate, HR=heart rate, GCS=Glasgow Coma Scale score, INR=international normalized ratio, AUROC=area under the receiver operating characteristics curve.

Table 2. New organ dysfunction based on initial vital signs, blood tests, and scores.

	New organ dysfunction (n=27)				
	Y	OR (95% CI)	Sn (%)	Sp (%)	ROC
Vital Signs:					
Tachypnoea (SIRS); n=4726	26	8.2 (1.4-338)	0.6	99	0.50
GCS <11; n=12	4	134 (27-540)	33	99	0.67
Tachycardia (SIRS); n=1374	14	3.8 (1.7-8.9)	1.0	99	0.50
Tachycardia (PELOD); n=88	2	5.7 (0.6-23)	2.3	99	0.51
Hypotension (SBP, SIRS); n=74	1	3.2 (0.1-20)	1.4	99	0.51
Hypotension (SBP, PELOD); n=154	3	5.0 (1.0-16)	2.0	99	0.51
Hypotension (MBP, PELOD); n=165	2	3.0 (0.3-12)	1.2	99	0.50
Blood Tests:					
Lactate ≥ 2 mmol/L; n=98	5	14 (4.3-41)	2.5	99	0.51
Lactate ≥ 4 mmol/L; n=11	1	23 (0.5-177)	9.1	99	0.54
INR ≥ 1.2 ; n=57	10	77 (29-187)	17	99	0.59
Elevated creatinine (PELOD); n=123	5	11 (3.4-32)	4.1	99	0.52
Platelet count 77-141; n=90	2	5.5 (0.6-22)	2.2	99	0.51
Platelet count ≤ 76 ; n=61	2	8.3 (0.9-34)	3.3	99	0.51
White cell count ≤ 2 ; n=76	2	6.6 (0.7-27)	2.6	99	0.51
Scores:					

SIRS; n=4733	26	8.0 (1.3-330.1)	0.5	99	0.50
qSOFA $\geq$ 1; n=4677	26	8.6 (1.4-352.9)	0.6	99	0.50
qSOFA $\geq$ 2; n=1357	15	4.5 (2.0-10.6)	1.1	99	0.50
qSOFA=3; n=5	2	165.0 (13.1-1483.2)	40	99	0.70
qPELOD $\geq$ 1 (SBP); n=253	9	13.7 (5.3-33.2)	3.6	99	0.52
qPELOD $\geq$ 1 (MBP); n=265	8	9.7 (3.6-23.5)	3.0	99	0.51

CI=confidence interval,

SIRS=Systemic Inflammatory Response Syndrome, PELOD=Pediatric Logistic Organ Dysfunction Score, SBP=systolic blood pressure, MBP=mean blood pressure, RR=respiratory rate, HR=heart rate, GCS=Glasgow Coma Scale score, INR=international normalized ratio, Y=yes, OR=odds ratio, CI=confidence interval, Sn=sensitivity, Sp=specificity, ROC=area under the receiver operating characteristics curve.

Table 3. Requirement for inotropic support and mechanical ventilation based on initial vital signs, blood tests, and scores.

	Inotropic support (n=5)					Mechanical ventilation (n=6)				
	Y	OR(95% CI)	Sn(%)	Sp(%)	ROC	Y	OR(95%CI)	Sn(%)	Sp(%)	ROC
Vital Signs:										
Tachypnoea (SIRS); n=4726	5	- (all)	0.1	100	0.50	6	- (all)	0.1	100	0.50
GCS <11; n=12	0	- (none)	0.0	99	0.50	3	689 (77-5606)	25	100	0.63
Tachycardia (SIRS); n=1374	3	5 (0.6-63)	25	100	0.63	3	3 (0.5-26)	25	100	0.63
Tachycardia (PELOD); n=88	0	- (none)	0.0	99	0.50	0	- (none)	0.0	99	0.50
Hypotension (SBP, SIRS); n=74	1	21 (0.4-215)	1.4	99	0.51	1	16 (0.4-152)	1.4	99	0.51
Hypotension (SBP, PELOD); n=154	2	27 (2.3-240)	1.3	100	0.51	1	7 (0.2-71)	0.6	99	0.50
Hypotension (MBP, PELOD); n=165	1	9 (0.2-93)	0.6	99	0.50	1	7 (0.2-66)	0.6	99	0.50
Blood Tests:										
Lactate ≥ 2 mmol/L; n=98	2	42 (3.5-373)	2.0	100	0.51	1	12 (0.3-114)	1.0	99	0.51
Lactate ≥ 4 mmol/L; n=11	1	155 (2.9-1734)	9.1	99	0.55	1	124 (2.4-1250)	9.1	99	0.55
INR ≥ 1.2 ; n=57	3	171 (19-2063)	5.3	100	0.53	3	114 (14-862)	5.3	100	0.53
Elevated creatinine (PELOD); n=123	1	12 (0.3-128)	0.8	99	0.50	1	10 (0.2-90)	0.8	99	0.50
Platelet count 77-141; n=90	1	17 (0.3-175)	1.1	99	0.51	1	13 (0.3-124)	1.1	99	0.51

Platelet count ≤ 76 ; n=61	0	- (none)	0.0	99	0.50	0	- (none)	0.0	99	0.50
White cell count ≤ 2 ; n=76	1	20 (0.4-209)	1.3	99	0.50	0	- (none)	0.0	99	0.50
Scores:										
SIRS; n=4733	5	- (all)	0.1	100	0.50	6	- (all)	0.1	100	0.50
qSOFA ≥ 1 ; n=4677	5	- (all)	0.1	100	0.50	6	- (all)	0.1	100	0.51
qSOFA ≥ 2 ; n=1357	3	5 (0.6-64)	0.2	100	0.50	3	3 (0.5-26)	0.2	99	0.50
qSOFA=3; n=5	0	- (none)	0.0	99	0.50	2	1034 (64-\$)	40	99	0.70
qPELOD ≥ 1 (SBP); n=253	2	15 (1.3-138)	0.8	99	0.50	4	47 (6.8-530)	1.6	100	0.50
qPELOD ≥ 1 (MBP); n=265	1	5.6 (0.1-57)	0.4	99	0.50	4	45 (6.5-504.)	1.5	100	0.50

CI=confidence interval, SIRS=Systemic Inflammatory Response Syndrome, PELOD=Pediatric Logistic Organ Dysfunction Score, SBP=systolic blood pressure, MBP=mean blood pressure, RR=respiratory rate, HR=heart rate, GCS=Glasgow Coma Scale score, INR=international normalized ratio, Y=yes, OR=odds ratio, CI=confidence interval, Sn=sensitivity, Sp=specificity, ROC=area under the receiver operating characteristics curve, \$=>10000.

Score	Variables used to calculate score	Outcomes measured	Setting
Systemic Inflammatory Response Syndrome (SIRS)(3)	2 of: Fever >35°C Tachycardia Tachypnoea Leukocytosis or leukopenia (must include either fever or leukocytosis)	Diagnosis of sepsis	ED ICU
Quick Sequential Organ Failure Assessment (qSOFA)(10)	3 of: Tachypnoea GCS score <11 Hypotension	Death or ICU admission / LOS ≥ 3 days or Hospital LOS ≥ 7 days	ED ICU
Quick Pediatric Logistic Organ Dysfunction-2 (qPELOD)(8)	3 of: Tachycardia GCS score <11 Hypotension	Death or ICU admission / LOS ≥ 3 days or Hospital LOS ≥ 7 days	ED ICU
Pediatric Logistic Organ Dysfunction-2 (PELOD-2)(11)	Any of: GCS score <11 Hypotension Elevated lactate Elevated creatinine Invasive ventilation Leukopenia Thrombocytopenia	Death	ICU

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