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Research paper

The 4-Hour Cairns Sepsis Model: A novel approach to predicting sepsis mortality at intensive care unit admission

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ABSTRACT

Background: Sepsis commonly causes intensive care unit (ICU) mortality, yet early identification of adults with sepsis at risk of dying in the ICU remains a challenge.
Objective: The aim of the study was to derive a mortality prediction model (MPM) to assist ICU clinicians and researchers as a clinical decision support tool for adults with sepsis within 4 h of ICU admission.
Methods: A cohort study was performed using 500 consecutive admissions between 2014 and 2018 to an Australian tertiary ICU, who were aged ≥18 years and had sepsis. A total of 106 independent variables were assessed against ICU episode-of-care mortality. Multivariable backward stepwise logistic regression derived an MPM, which was assessed on discrimination, calibration, fit, sensitivity, specificity, and predictive values and bootstrapped.
Results: The average cohort age was 58 years, the Acute Physiology and Chronic Health Evaluation III-j severity score was 72, and the case fatality rate was 12%. The 4-Hour Cairns Sepsis Model (CSM-4) consists of age, history of renal disease, number of vasopressors, Glasgow Coma Scale, lactate, bicarbonate, aspartate aminotransferase, lactate dehydrogenase, albumin, and magnesium with an area under the receiver operating characteristic curve of 0.90 (95% confidence interval = 0.84–0.95, $p < 0.00001$), a Nagelkerke R^2 of 0.51, specificity of 0.94, a negative predictive value of 0.98, and almost identical odds ratios during bootstrapping. The CSM-4 outperformed existing MPMs tested on our data set. The CSM-4 also performed similar to existing MPMs in their derivation papers whilst using fewer, routinely collected, and inexpensive variables.
Conclusions: The CSM-4 is a newly derived MPM for adults with sepsis at ICU admission. It displays excellent discrimination, calibration, fit, specificity, negative predictive value, and bootstrapping values whilst being easy to use and inexpensive. External validation is required.

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1. Introduction

Sepsis is defined as "life-threatening organ dysfunction due to a dysregulated host response to infection".[1] It is a leading cause of death globally.[2,3] The annual incidence of sepsis among adult patients in Australian and New Zealand intensive care units (ICUs) is 77 cases per 100000 population, with an in-hospital mortality of 37.5%, that is, 17000 cases and more than 6000 deaths.[4] It has an estimated cost per episode of AUD 39300.[5] Despite this, early identification of adults with sepsis at risk of dying in the ICU remains a challenge.[6,7]

Mortality prediction models (MPMs) estimate risk of death in a patient population. As a clinical decision support tool, they can assist clinicians in patient risk stratification, prognostication, patient outcome discussions, and shared decision-making. They can also be used by researchers to compare clinical outcomes, compare patient cohorts in randomised control trials, and evaluate ICUs and improve safety and quality via the standardised mortality ratio.[8–10] Good MPMs are assessed on discrimination, commonly measured using the area under the receiver operating characteristic curve (AUROC), calibration as measured by a goodness-of-fit statistic such as the Hosmer–Lemeshow c-statistic (Hosmer–Lemeshow goodness of fit [HLGOF]), and global model fit as measured by the Nagelkerke R^2 statistic (NR2). They should also be applicable to all patients, clinically easy to use, and calculated on inexpensive and routinely collected variables specifically for the population of interest (i.e., sepsis).[9,11,12]

Several MPMs already exist in critically ill patients. However, although these MPMs may have disease modifier codes to prognosticate different diagnoses, there currently exists no MPM specifically for adults with sepsis at ICU admission who meet the aforementioned criteria of a "good" MPM. More importantly, existing MPMs were never designed to be used on individual patients; rather, they are designed for cohort use only.[13,14] Thus, the aim of this study was to derive an MPM, which meets the aforementioned criteria of a good MPM, for use as a clinical decision support tool on adults with sepsis by ICU clinicians within 4 hours of ICU admission.

2. Materials and methods

A retrospective cohort study was performed with data collection at Cairns Hospital, a 531-bed tertiary referral centre serving a population of approximately 240000.[15]

2.1. Ethics statement

The Human Research Ethics Committee of the Cairns and Hinterland Health Service District provided ethical approval for the study (HREC/17/QCH/93/AMO2).

2.2. Inclusion criteria

The first 500 consecutive adults (aged ≥18 years) admitted to the ICU of Cairns Hospital between 01/01/2014 and 01/06/2018 with a diagnosis of sepsis were included. Sepsis had to be the primary admission diagnosis as per the Sepsis-3 definitions[1] and Acute Physiology and Chronic Health Evaluation (APACHE) III-j diagnostic codes 501–504: nonurinary sepsis, urinary sepsis, nonurinary sepsis with shock, and urinary sepsis with shock, respectively.[16] If patients were admitted on several occasions, only their first admission was included. There were no exclusion criteria.

2.3. Data collection

Data were collected from the Cairns Hospital ICU electronic medical record database (MetaVision®; *iMDsoft*, Tel Aviv, Israel) by four clinicians (S.H., S.S., T.G., J.B.) using a standardised data sheet. To ensure consistency, variable definitions were created (Table 1). Once the data were collected, a data cleaning process was undertaken to minimise human error manually, reviewing inputs greater than 2 standard deviations away from the mean. All variables available within 4 hours of ICU admission were collected to ensure a thorough investigation of the research question, creating a total independent variable pool of 106. Four hours was selected as most laboratory and point-of-care testing results, invasive admission procedures and admission clerking notes were available at this time. This allowed for optimal data collection. Collecting earlier would have resulted in an increase in missing data. Collecting later would compromise the models' use "on admission", would not provide early information to clinicians, and would not reflect changes that occur after early ICU interventions. Variables were categorised into Predisposition, Insult, Response, and Organ Dysfunction (PIRO) variables as per the validated PIRO sepsis staging model.[17] Our dependent variable was ICU episode-of-care mortality.

2.4. Statistical analysis

Independent variables that had fewer than 350 inputs owing to missing data were omitted from our analysis. These were often variables such as troponins, C-reactive protein, and coagulation profiles that are not routinely collected from all patients. Univariate logistic regression using ICU episode-of-care mortality as the dependent variable was performed as a sorting mechanism to reduce the number of independent variables of interest before the final analysis. Independent variables with $p > 0.1$ were eliminated. The remaining independent variables were tested for zero-order correlations, defined as Pearson correlation coefficient (r) < -0.6 or >0.6 and $p < 0.05$. A choice between variables was made if any zero-order correlations were identified.

Multivariable backward stepwise logistic regression was performed on the remaining variables to identify variables that best correlated with ICU episode-of-care mortality. The probability for the regression was set at $p < 0.01$ for entry and $p > 0.05$ for removal. The level of significance for the final independent variables was set to $p < 0.05$.

Model discrimination was tested using AUROC, calibration was tested using HLGOF, and the models' overall fit was tested using NR2. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated, with a cut-off in probability of death being 50% for the latter. A logistic regression bootstrap procedure was deployed to further estimate internal validation based on 2000 samples using a simple sampling method. This procedure estimated the average odds ratio (OR), with 95% confidence interval, and average p-value obtained from logistic regression of all 2000 samples. Statistical analysis was performed using IBM SPSS® Statistics for Windows, version 27.0, software (IBM Corp., Armonk, NY).

3. Results

Overall, the ICU case fatality rate was 12% (n = 59), the average cohort APACHE-III-j severity score was 72, and the average age of our cohort was 58 years. Of these, 54% were men (n = 272), and 35% (n = 176) identified as Aboriginal or Torres Strait Islanders (Tables 2 and 3). A significant number of patients were transferred to our centre from peripheral hospitals (n = 194, 39%) and had significant pre-existing comorbidities such as smoking (n = 243, 53%),

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Table 1
Variable definitions.

- Presumed infection: assumed when concomitant orders exist for both blood cultures and antibiotics within the time period around suspected infection.[40]
- SOFA baseline/admission: needs to be a rise in SOFA score >2 to meet admission criteria for study.[40]
- Mortality: if the patient died during an ICU admission episode.
- Smoker: either current or former with ≥10 cigarettes per day.
- History of alcohol use: if the patient has ≥4 standard drinks of alcohol per day.
- From interhospital transfer: if the patient was admitted elsewhere and then transferred to Cairns.
- From emergency department: if the patient was admitted to the ICU straight from the emergency department.
- From operating theatre: if the patient was admitted to the ICU within 24 h after surgery.
- From hospital ward: if the patient was admitted to the ICU from the hospital ward (having spent at least 4 h there).
- History of sepsis: any previous diagnosis of sepsis as per Australian ICU diagnostic coding.
- History of cardiovascular disease:[41] ischaemic heart disease, stroke, heart failure (major adverse cardiac events).
- History of respiratory disease:[42] chronic obstructive or restrictive lung disease.
- History of renal disease.[43]: chronic kidney disease or on dialysis
- History of haematological cancer:[43] lymphoma, leukaemia, myeloma.
- History of gastrointestinal disease:[43] cirrhosis, hepatic failure.
- History of diabetes: type 1 or type 2 diabetes.
- History of metastatic cancer:[43] malignancy with metastatic disease.
- History of being immunocompromised:[43] HIV/AIDS, steroids, chemotherapy, immunosuppressant medication (e.g., methotrexate, azathioprine, etc).
- Admit night: the patient was admitted after 6 pm and before 8 am.
- Site of infection, lungs/genitourinary/neurological/bones or joints/soft tissue/abdomen/other: primary site of suspected infection.
- Bacteraemia: positive blood cultures with grown organisms.
- Recent arrest: cardiac/respiratory arrest in the last 24 h
- All clinical variables/laboratory tests/procedures: taken ±4 h from time of ICU admission (take closest to admission when >1 in this period)
- Albumin = calcium-corrected version obtained.
- Fibrinogen − derived fibrinogen, not clotted.
- Number of vasopressors: number of vasopressors patient was on ± 4 h from time of ICU admission.
- Admission antibiotics were antibiotics started either on or within 4 h from time of ICU admission.
- Arrhythmia: anything nonsinus excluding sinus bradycardia, sinus tachycardia, premature atrial or ventricular contractions.

hazardous drinking (n = 116, 25%), and cardiovascular disease (n = 161, 32%). Whilst the commonest source of infection was pulmonary (33%, n = 163), the commonest bug isolated was *Escherichia coli* (n = 68, 14%).

3.1. 4-Hour Cairns Sepsis Model

The univariate logistic regression screened out 60 independent variables as unlikely to have a strong correlation with mortality. There were no zero-order correlations between the remaining 42 independent variables, so they were put into the multivariable backward stepwise regression. This resulted in a final model with 10 independent variables for the 4-Hour Cairns Sepsis Model (CSM-4) (Table 4). The CSM-4 contained two predisposition variables, seven acute physiology variables, and one organ dysfunction variable that had an independent significant association with ICU episode-of-care mortality for patients with sepsis within 4 hours of ICU admission (Table 4). These are age (OR = 1.4 [1.0–1.9], $P = 0.045$), history of renal disease (OR = 3.5 [1.2–10], $P = 0.021$), number of vasopressors on admission (OR = 2.8 [1.6–5.1], $P < 0.001$), Glasgow Coma Scale (GCS) (OR = 0.88 [0.81–0.96], $P = 0.004$), lactate (OR = 1.5 [1.1–1.8], $P = 0.024$), bicarbonate (OR = 1.2 [1.1–1.3], $P = 0.003$), admission aspartate aminotransferase (OR = 0.80 for every relative 50 units/L decrease [0.69–0.92], $P = 0.002$), admission lactate dehydrogenase (OR = 1.2 for every relative 50 units/L increase [1.1–1.3], $P < 0.001$), albumin (OR = 0.86 [0.79–0.95], $P = 0.002$), and admission magnesium (OR = 1.4 for every relative 0.1 mmol/L increase [1.2–1.7], $P < 0.001$). For the complete model, the AUROC was 0.90 (0.84–0.95), the HLGOF was 0.081, and the NR2 was 0.51. The sensitivity was 0.79, specificity was 0.94, NPV was 0.98, and PPV was 0.54, with a cut-off in probability of death being 50%. The bootstrap procedure confirmed similar ORs to the ones found in the original data set (Table 4).

3.2. Comparison of the CSM-4 with other MPMs

The performance of the CSM-4 was analysed against the performance of the other available MPMs in their original derivation papers (Table 5). The CSM-4 had the highest discrimination (AUC = 0.90, $p < 0.001$) and overall model fit (NR2 = 0.51), with good calibration (HLGOF = 0.081). It was the most recently created score (2020) and used the third least variables (10 vs. 8 in the sequential organ failure assessment (SOFA) score and 3 in the quick SOFA (qSOFA) score). The CSM-4 was also compared with other available MPMs using our patient data set (Table 6). When applied to our patient data set, the CSM-4 had the highest discrimination and closest calibration outperforming all other MPMs available for comparison.

4. Discussion

The CSM-4 is a newly derived MPM for ICU clinician use, after external validation, as a clinical decision support tool to assist in the prediction of an individual's mortality risk from sepsis at ICU admission. It displays good discrimination, calibration, model fit, specificity, and NPV. It is easy to use, with only 10 routinely collected and easily accessible variables, with no complex calculations or interventions needed.

4.1. MPMs: an overview

The increasing use of electronic medical records and technological advancements have created large amounts of data. Extracting and analysing useful data can enable progress in clinical decision-making, ultimately improving patient outcomes.[18] Despite sepsis having both high ICU incidence and case fatality rate, the identification of patients with sepsis at risk of dying remains a challenge, and information regarding early predictive factors for mortality is limited.[19] The rapid, precise prediction of poor outcomes via an MPM may support clinicians in clinical decision-making.[18] One such clinical use of an MPM is patient risk stratification, wherein patients at highrisk of mortality could be considered for escalation of care or more aggressive therapy, considered for closer monitoring for clinical deterioration, and considered for advance care planning discussions.[20,21] Furthermore, a good MPM may assist clinicians in patient outcome discussions and informing

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Table 2
Binary independent variables describing patient admission characteristics.

Independent variables (binary)	Patient statistics		
	Number of patients	Distribution	%
Predisposition			
Male gender	500	272	54
Indigenous	500	176	35
From interhospital transfer	500	194	39
From emergency department	500	158	32
From nursing home	500	0	0.00
From surgical theatre	500	6	1.2
From hospital ward	499	142	29
>4 standard drinks of alcohol/day	461	116	25
Smoker >10 cigarettes/day	460	243	53
History of sepsis	430	86	20
History of cardiovascular disease	497	161	32
History of respiratory disease	497	91	18
History of renal disease	497	95	19
History of haematological cancer	496	45	9.1
History of gastrointestinal disease	497	43	8.7
History of diabetes	497	176	35
History of metastatic cancer	498	42	8.4
History of being immunocompromised	498	70	14
Admitted at night	500	307	61
Recent cardiac arrest	500	15	3.0
Statin use	498	138	28
Infection			
Site of infection, lungs	492	163	33
Site of infection, genitourinary	492	105	21
Site of infection, neuro	492	5	1.0
Site of infection, bones/joints	492	13	2.6
Site of infection, soft tissue	492	96	19
Site of infection, abdomen	492	67	14
Gram-negative bacteria	439	206	47
Gram-positive bacteria	440	152	35
Bacterial	443	314	71
Fungal	443	17	3.8
Viral	442	32	7.2
Bacteraemia	478	198	41
E. coli	500	68	14
S. aureus	500	60	12
Methicillin-resistant *S. aureus*	500	17	3.4
P. aeruginosa	500	41	8.2
K. pneumonia	500	24	4.8
Influenza A	500	17	3.4
B. pseudomallei	500	17	3.4
S. pyogenes	500	26	5.2
Leptospirosis	500	11	2.2
S. pneumonia	500	15	3.0
P. jirovecii	500	6	1.2
Organ dysfunction			
Dose of vasopressors >1 mcg/kg/min	389	160	41
Admission antibiotics	499	488	98
Intubated	499	101	20
Peripherally inserted central catheter	498	149	30
Central venous line	500	206	41
Arterial line	500	413	83
Nasogastric tube	500	101	20
Indwelling catheter	500	418	84
Continuous renal replacement therapy	497	111	22

care discussions and shared decision-making. They may also assist researchers in comparing patient cohorts in randomised control trials[9] and healthcare governance by allowing evaluation of ICU performance and improvement of safety and quality of ICU care via calculation of the standardised mortality ratio.[22,23]

Before an MPM is considered for use, it should be assessed on a discrimination measurement such as the AUROC, a calibration measurement such as a goodness-of-fit statistic such as the HLGOF, and a global model fit statistic such as NR2. They should also be applicable to all patients, clinically easy to use, and calculated on cheap and routinely collected variables specifically for the population of interest (i.e., sepsis).[9,11,12] Minimal data requirements lighten the burden of implementation in a clinical setting and broaden its application.[24] Before use, MPMs should also be appropriately externally validated. To remain relevant, risk scores need to be updated to reflect evolutions in diagnostics and therapeutics.[18,24]

4.2. Assessing current MPMs

There are many MPMs described in the literature for use in the ICU. These can be divided into general and disease-specific ones (i.e., sepsis). General MPMs include the APACHE,[25] simplified acute physiology score (SAPS)[26] and MPM scores,[27] whereas the most

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Table 3
Continuous independent variables describing patient admission characteristics.

Independent variables (continuous)	Distribution	
	Number of patients	Mean (standard deviation); median (interquartile range)
Predisposition		
Age (years)	500	58 (16); 60 (48–69)
Body mass index	494	30 (9.1); 28 (23–33)
Infection		
Number of organisms	478	0.98 (0.83); 1.0 (0–1)
Response		
Heart rate (beats per minute)	499	100 (23); 99 (84–115)
Systolic blood pressure (mmHg)	499	109 (21); 07 (95–121)
Mean arterial blood pressure (mmHg)	499	74 (14.6); 73 (65–83)
Diastolic blood pressure (mmHg)	499	61 (14.4); 60 (51–68)
Temperature (degree Celsius)	498	37 (0.98); 37 (37-37)
Respiratory rate (breaths per minute)	499	22 (6.6); 20 (17–25)
Oxygen saturation (percentage)	498	96 (3.9); 97 (95–99)
Glasgow Coma Scale score (out of 15)	496	13 (4.2); 97 (14–15)
Blood sugar level (mmol/L)	488	7.7 (3.5); 6.6 (5.3–9)
Number of vasopressors	459	1.03 (0.78); 1 (1-1)
Dose of vasopressor, more than 1 mcg/min	389	1.3 (0.66); 1 (1–2)
Fraction of inspired oxygen (%)	474	42 (26); 30 (21–50)
Lactate (mmol/L)	448	2.4 (2.1); 1.8 (1.1–3)
Alveolar–arterial gradient (mmHg)	217	183 (179); 127 (54–292)
pH	462	7.3 (0.13); 7.4 (7.3–7.4)
Partial pressure of CO_2 (mmHg)	459	36 (12); 34 (28–41)
Bicarbonate (mmol/L)	464	19 (5.5); 19 (16–22)
Base excess (mEq/L)	462	−6.3 (6.4); −5.2 (−9 -(-2.5))
Anion gap (mEq/L)	439	9.8 (4.3); 9 (7–12)
Partial pressure of O_2 (mmHg)	446	93 (54); 81 (70–99)
Partial pressure of O_2:fraction of inspired O_2	420	282 (137); 285 (166–384)
Oxygenated haemoglobin (%)	421	92 (10); 94 (92–96)
Carboxylated haemoglobin (%)	389	0.74 (0.68); 0.5 (0.3–1)
Methaemoglobin (%)	355	0.38 (0.53); 0.3 (0.2–0.4)
Haemoglobin (g/L)	424	107 (24); 107 (89–124)
Red cell count (10^{12}/L)	418	3.7 (0.82); 3.7 (3.1–4.3)
Haematocrit (L/L)	420	0.33 (0.71); 0.32 (0.27–0.37)
Mean cell volume (fL)	417	88 (7.6); 88 (83–93)
White cell count (10^9/L)	415	17 (12); 14 (8.4–22)
Neutrophils (10^9/L)	416	14 (10); 11 (6.4–19)
Eosinophils (10^9/L)	416	0.15 (1.9); 0 (0–0.4)
Basophils (10^9/L)	416	0.018 (0.041); 0.0 (0.0–0.02)
Monocytes (10^9/L)	414	0.85 (1.2); 0.6 (0.3–1.2)
Lymphocytes (10^9/L)	415	1.2(1.5); 0.82 (0.42–1.4)
Platelets (10^9/L)	397	184 (113); 171 (103–245)
C-reactive protein (mg/L)	167	195 (133); (80–290)
Troponin I (mcg/L)	117	1.7 (5.4); 0.12 (0.041–0.38)
Prothrombin time (s)	349	18 (10); 16 (14–18)
Activated partial thromboplastin Time (s)	345	40 (15); 37 (32–43)
International normalised ratio	348	1.6 (0.81); 1.4 (1.3–1.6)
Fibrinogen (mg/dL)	346	6.6 (2.5); 6.5 (4.8–8.2)
Aspartate aminotransferase (U/L)	419	136 (343); 51 (24–109)
Alanine aminotransferase (U/L)	418	71 (146); 33 (18–63)
Gamma-glutamyl transferase (U/L)	424	75 (101); 48 (25–94)
Alkaline phosphatase (U/L)	424	110 (94); 85 (61–126)
Lactate dehydrogenase (U/L)	410	466 (633); 330 (243–452)
Conjugated bilirubin (μmol/L)	329	17 (23); 8 (8–18)
Total bilirubin (μmol/L)	423	29 (32); 19 (13–31)
Albumin (g/L)	408	25 (5.2); 25 (21–28)
Protein (mg/L)	424	56 (9.51); 55 (49–62)
Creatinine (μmol/L)	424	219 (247); 29 (80–262)
Urea (mmol/L)	403	13 (12); 9.4 (5.6–17)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	354	41 (27); 38 (16–63)
Osmolality (mmol/kg)	416	288 (16); 287 (279–295)
Calcium (mmol/L)	412	2.2 (0.2); 2.2 (2.1–2.3)
Phosphate (mmol/L)	423	1.4 (0.77); 1.2 (0.91–1.8)
Magnesium (mmol/L)	424	0.77 (0.20); 0.74 (0.65–0.87)
Sodium (mmol/L)	430	134 (5.1); 135 (131–137)
Potassium (mmol/L)	427	4.2 (0.82); 4.1 (3.7–4.6)
Chloride (mmol/L)	427	104 (6.4); 104 (100–108)
Organ dysfunction		
Minute ventilation (mL/min)	98	7.8 (2.0); 7.8 (6.5–9.0)
Urine output at 4 h (mL)	495	378 (430); 255 (100–517)

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Table 4
4-Hour cairns sepsis model (CSM-4).

Admission variables	Univariate analysis			Multivariate analysis (n = 344)	
	No. of patients	P-value	Odds ratio (95% CI)	P-value[a]	Odds ratio (95% CI)[a]
Predisposition					
Age (decade)	500	0.018	1.3 (1.0–1.5)	0.045/0.043	1.4 (1.0–1.9)/1.4 (1.0–2.2)
Male gender	500	0.42	1.3 (0.72–2.2)		
Indigenous	500	0.82	0.94 (0.53–1.7)		
Socio-economic status	416	0.44	1.0 (0.99–1.0)		
From interhospital transfer	500	0.41	0.79 (0.44–1.4)		
From emergency department	500	0.43	0.78 (0.43–1.4)		
From nursing home	500	–	–		
From surgical theatre	500	1.00	0.00 (0.00–∝)		
From hospital ward	499	0.059	1.7 (0.98–3.0)		
>4 standard drinks of alcohol per day	461	0.64	0.85 (0.42–1.7)		
Smoker	460	0.97	1.0 (0.56–1.8)		
History of sepsis	430	0.81	0.91 (0.40–2.0)		
History of cardiovascular disease	497	0.066	1.7 (0.97–3.0)		
History of respiratory disease	497	0.22	1.5 (0.78–2.9)		
History of renal disease	497	0.17	1.6 (0.83–3.0)	0.021/0.027	3.5 (1.2–10)/3.5 (0.92–15)
History of haematological cancer	496	0.19	1.7 (0.77–3.9)		
History of gastrointestinal disease	497	0.99	1.0 (0.38–2.6)		
History of diabetes	497	0.47	1.2 (0.70–2.2)		
History of metastatic cancer	498	0.14	1.9 (0.82–4.3)		
History of being immunocompromised	498	0.28	1.5 (0.73–3.0)		
Admitted at night	500	0.43	1.3 (0.71–2.2)		
BMI	494	0.93	0.99 (0.97–1.0)		
Recent cardiac arrest	500	0.0000030	13 (4.5–38)		
Infection					
Site of infection, lungs	492	0.088	1.6 (0.93–2.8)		
Site of infection, genitourinary	492	0.072	0.47 (0.21–1.1)		
Site of infection, neuro	492	1.00	0.00 (0.00-∝)		
Site of infection, bones/joints	492	1.00	0.00 (0.00–∝)		
Site of infection, soft tissue	492	0.81	1.1 (0.55–2.1)		
Site of infection, abdomen	492	0.39	1.4 (0.66–2.9)		
Gram-negative bacteria	439	0.78	0.92 (0.51–1.7)		
Gram-positive bacteria	440	0.91	1.0 (0.56–1.9)		
Bacterial	443	0.35	1.4 (0.70–2.7)		
Fungal	443	0.026	3.4 (1.2–10)		
Viral	442	0.69	0.78 (0.23–2.7)		
Bacteraemia	478	0.72	1.1 (0.63–2.0)		
No. of organisms cultured	478	0.84	1.3 (0.96–1.8)		
Response					
Heart rate (beats per minute)	499	0.19	1.0 (1.0–1.0)		
Systolic blood pressure (mmHg)	499	0.067	0.99 (0.97–1.0)		
Mean arterial blood pressure (mmHg)	499	0.27	0.99 (0.97–1.0)		
Diastolic blood pressure (mmHg)	499	0.29	0.99 (0.97–1.0)		
Temperature (degree Celsius)	498	0.0000090	0.51 (0.38–0.69)		
Respiratory rate (breaths per minute)	499	0.058	0.96 (0.92–1.0)		
Oxygen saturation (percentage)	498	0.0040	0.92 (0.87–0.97)		
Glasgow Coma Scale score (out of 15)	496	<0.000001	0.85 (0.81–0.90)	0.0039/0.0030	0.88 (0.81–0.96)/0.88 (0.79–0.96)
Blood sugar level (mmol/L)	488	0.43	1.0 (0.96–1.1)		
Fraction of inspired oxygen (%)	474	0.000096	1.0 (1.0–1.0)		
Lactate (mmol/L)	448	<0.000001	1.4 (1.3–1.6)	0.0024/<0.001	1.5 (1.1–1.8)/1.5 (1.2–1.9)
Alveolar–arterial gradient (mmHg)	217	0.000006	1.0 (1.0–1.0)		
pH	462	<0.000001	0.010 (0.00–0.060)		
Partial pressure of CO_2 (mmHg)	464	0.0040	1.0 (1.0–1.0)		
Bicarbonate (mmol/L)	464	0.017	0.94 (0.90–0.99)	0.0034/0.0030	1.2 (1.1–1.3)/1.2 (1.1–1.3)
Base excess (mEq/L)	462	0.000073	0.93 (0.89–0.96)		
Anion gap (mEq/L)	439	0.0060	1.1 (1.0–1.2)		
Partial pressure of O_2 (mmHg)	446	0.63	1.0 (1.0–1.0)		
Partial pressure of O_2:fraction of inspired O_2	420	0.0010	1.0 (0.99–1.0)		
Oxygenated haemoglobin (%)	421	0.67	0.99 (0.97–1.0)		
Carboxylated haemoglobin (%)	389	0.51	1.2 (0.77–1.7)		
Methaemoglobin (%)	355	0.67	0.82 (0.33–2.0)		
Haemoglobin (g/L)	371	0.59	1.0 (0.99–1.0)		
Red cell count (10^{12}/L)	418	0.76	0.95 (0.66–1.4)		
Haematocrit (L/L)	420	0.72	0.47 (0.01–29)		
Mean cell volume (fL)	417	0.42	1.0 (0.98–1.1)		
White cell count (10^9/L)	415	0.57	1.0 (0.98–1.0)		
Neutrophils (10^9/L)	416	0.44	1.0 (0.98–1.0)		
Eosinophils (10^9/L)	416	0.79	0.93 (0.55–1.6)		
Basophils (10^9/L)	416	0.14	71 (0.26–1.9 × 10^4)		
Monocytes (10^9/L)	414	0.17	1.1 (0.95–1.4)		
Lymphocytes (10^9/L)	415	0.81	1.1 (0.98–1.3)		
Platelets (10^9/L)	397	0.086	1.0 (0.99–1.0)		

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Table 4 (*continued*)

Admission variables	Univariate analysis			Multivariate analysis (n = 344)	
	No. of patients	P-value	Odds ratio (95% CI)	P-value[a]	Odds ratio (95% CI)[a]
C-reactive protein (mg/L)	167	0.093	1.0 (1.0–1.0)		
Troponin I (mcg/L)	117	0.041	1.1 (1.0–1.2)		
Prothrombin time (s)	349	0.0020	1.0 (1.0–1.1)		
Activated partial thromboplastin time (s)	345	0.00011	1.0 (1.0–1.1)		
International normalised ratio	348	0.0010	1.7 (1.3–2.3)		
Fibrinogen (mg/dL)	346	0.79	1.0 (0.90–1.1)		
Aspartate aminotransferase (U/L) – change >50 units	419	0.0060	1.0 (1.0–1.1)	0.0022/<0.001	0.80 (0.69–0.92)/0.80 (0.65–0.90)
Alanine aminotransferase (U/L)	418	0.16	1.0 (1.0–1.0)		
Gamma-glutamyl transferase (U/L)	424	0.65	1.0 (1.0–1.0)		
Alkaline phosphatase (U/L)	424	0.10	1.0 (1.0–1.0)		
Lactate dehydrogenase (U/L) – change >50 units	410	0.00042	1.0 (1.0–1.1)	0.00027/<0.001	1.2 (1.1–1.3)/1.2 (1.1–1.3)
Conjugated bilirubin (μmol/L)	329	0.0010	1.0 (1.0–1.0)		
Total bilirubin (μmol/L)	423	0.0010	1.0 (1.0–1.0)		
Albumin (g/L)	408	0.000074	0.87 (0.81–0.93)	0.0022/0.010	0.86 (0.79–0.95)/0.86(0.73–0.96)
Protein (mg/L)	424	0.014	0.96 (0.93–0.99)		
Creatinine (μmol/L)	424	0.18	1.0 (1.0–1.0)		
Urea (mmol/L)	403	0.045	1.0 (1.0–1.0)		
Estimated glomerular filtration rate (mL/min/1.73 m^2)	354	0.14	0.99 (0.98–1.0)		
Osmolality (mmol/kg)	416	0.020	1.0 (1.0–1.0)		
Calcium (mmol/L)	412	0.10	0.29 (0.07–1.3)		
Phosphate (mmol/L)	423	<0.000001	2.4 (1.8–3.4)		
Mg_0.1 – change >0.1 unit	424	0.000014	1.3 (1.2–1.5)	0.00081/<0.001	1.4 (1.2–1.7)/1.4 (1.2-)
Sodium	430	0.94	1.0 (0.94–1.1)		
Potassium	427	0.018	1.5 (1.1–2.0)		
Chloride	427	0.12	0.97 (0.92–1.0)		
Organ dysfunction					
No. of vasopressors	499	<0.000001	3.3 (2.3–4.7)	0.00066/<0.001	2.8 (1.6–5.1)/2.8 (1.5–7.3)
Antibiotics on admission	499	0.51	0.60 (0.13–2.8)		
Intubated	499	<0.000001	5.9 (3.3–10)		
Minute ventilation	98	0.80	0.97 (0.78–1.2)		
Peripherally inserted central catheter	498	0.42	0.78 (0.42–1.4)		
Central venous line	500	0.0070	2.1 (1.2–3.6)		
Arterial line	500	0.24	1.7 (0.72–3.8)		
Nasogastric tube	500	0.0000040	3.9 (2.2–6.8)		
Indwelling catheter	500	0.90	0.96 (0.46–2.0)		
Continuous renal replacement therapy	499	0.0080	2.6 (1.3–5.4)		
Urine output over 4 h – change of 50 mL	487	0.00023	0.88 (0.82–0.94)		

CI = confidence interval.

[a] The first value is from the original data set. The second value (after forward slash) is the average outcome from regression of 2000 bootstrap samples.

commonly used and well-researched sepsis-specific scores are the SOFA[28] and qSOFA score.[1] Although general MPMs have their strengths, they are not sepsis-specific investigate variables such as organ dysfunction or acute physiology in isolation.[29] The accuracy of general MPM use in patient subgroups (i.e., sepsis) is therefore suboptimal, and disease-specific scoring systems are ideal. Furthermore, general MPMs use not only more variables but also those that are not routinely collected or easily accessible. Clinicians are unlikely to use complex MPMs that require collection of extensive or expensive information that impedes workflow.[21,22] The sepsis-specific SOFA score was developed over 20 years ago by expert consensus. Although it can predict mortality based on organ dysfunction variables, this is not what it was developed for as sepsis mortality prediction should not be based on measuring organ dysfunction alone.[24] Furthermore, the SOFA score requires numerous calculations and invasive tests that may dissuade clinician use.[30] The qSOFA score was designed as a ward-based sepsis screening tool rather than as an ICU MPM.[1] When applied to adults with sepsis at ICU admission, the qSOFA was not an effective ICU MPM, and hence, its use may be limited outside its intended scope. Furthermore, a literature review evaluating all ICU MPMs investigated 94 studies on 240 assessments of 118 MPMs found that the AUROC of MPMs ranged markedly from 0.43 to 0.98 (median = 0.77) and that most documented MPMs have limited clinical utility.[22] Overall, the ideal sepsis MPM therefore remains to be created.[13,14,31]

Table 5
Comparison between CSM-4 and the original articles of other MPMs.

MPMs	AUROC	Nagelkerke R^2	HLGOF	Year of creation	No. of patients	No. of variables
CSM-4 hr	0.90, p = 1.5×10^{-16}	0.51	0.081	2020	500	10
APACHE-IV	0.88, p = not given	Not given	0.80	2006	131,618	142
SOFA	0.88, p = not given	Not given	0.80	1996	1449	8
SAPS-III	0.85, p = not given	Not given	0.39	2005	16,784	20
MPM_0-III	0.82, p = not given	Not given	0.31	2007	124,855	16
qSOFA	0.61, p = not given	Not given	Not given	2016	148,907	3

APACHE = Acute Physiology and Chronic Health Evaluation; CSM-4 = 4-Hour Cairns Sepsis Model; SOFA = seequential organ failure assessment socre; SAPS = simplified acute physiology score; qSOFA = quick SOFA score; MPM = mortality prediction model; HLGOF = Hosmer–Lemeshow goodness of fit; AUROC = area under the receiver operating characteristic curve.

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Table 6
Comparison of other MPMs with CSM-4 using our data set.

MPMs	AUROC (95% CI)	Nagelkerke R^2	HLGOF	P-value	No. of variables
CSM-4 hr	0.90 (0.84–0.95)	0.51	0.081	1.5×10^{-16}	10
APACHE-II	0.69 (0.59–0.79)	0.12	0.59	7.4×10^{-8}	17
APACHE-III-j	0.77 (0.69–0.85)	0.20	0.80	4.8×10^{-17}	26
SOFA	0.78 (0.72–0.85)	0.20	0.54	1.4×10^{-9}	8
SAPS-II	0.81 (0.75–0.87)	0.24	0.19	7.6×10^{-11}	17
MPM II-24 hr	0.82 (0.72–0.85)	0.26	0.50	6.7×10^{-7}	15
qSOFA	0.60 (0.50–0.70)	0.017	0.20	0.062	3

APACHE = Acute Physiology and Chronic Health Evaluation; CSM-4 = 4-Hour Cairns Sepsis Model; MPM = mortality prediction model; HLGOF = Hosmer–Lemeshow goodness of fit; AUROC = area under the receiver operating characteristic curve; CI = confidence interval.

4.3. 4-Hour Cairns Sepsis Model

The internal validation of the CSM-4 shows excellent discrimination, calibration, and overall performance well above the median ICU MPM AUROC of 0.77.[9,22] Furthermore, the bootstrap procedure produced similar ORs to the original data set, suggesting that overfitting is not a major problem in the presented CSM-4. Derived in 2020, the CSM-4 is the most recent MPM. It uses routinely collected variables that are all available within 4 hours of ICU admission, without any need for overly invasive testing or complex calculations, making it clinically easy to use. In terms of cost, the collection of details such as age, history of renal disease, number of vasopressors used, and GCS requires simple beside clinical history taking, examination and routine laboratory costsmaking this a relatively inexpensive MPM to use.

Sepsis is a complex and heterogeneous syndrome. The PIRO concept has been validated as a way of sifting through the complexity and staging sepsis. Each of the four PIRO components predict in-hospital mortality, but they provide greater predictive accuracy when combined.[17] True to this finding, three of the four components of the PIRO model, namely, predisposition, physiological response, and organ dysfunction variables, were included in the CSM-4. Sepsis mortality, therefore, may be suboptimally predicted by organ dysfunction scores, such as the SOFA, or predominantly acute physiological scores, such as the general MPMs, alone.[17] The presence of acute hepatic, neurological, and cardiovascular system derangement was included in the final model, reaffirming the significance of multiorgan failure as a hallmark of critically unwell sepsis. The links between increasing age,[32] serum lactate levels,[1,2] serum lactate dehydrogenase levels[33] vasopressor use,[34] a history of renal disease[35], decreasing GCS score[1,2], and albumin levels[36] with sepsis mortality are already well described in the literature. Whilst to the best of our knowledge, there are no studies linking either increasing serum bicarbonate or serum magnesium levels to sepsis mortality, increased serum bicarbonate and magnesium levels independently predict ICU mortality. Reasons for this are unknown, but may include overly aggressive replacement in those who are already at high risk of dying.[37,38] Decreasing serum aspartate aminotransferase levels were also a predictor of sepsis mortality. Again, although the cause of this is unknown, patients with a history of renal disease are known to have reduced serum transaminase levels.[39] Further research into the pathophysiology of how the statistically significant variables predict sepsis mortality may broaden clinicians' understanding of sepsis diagnosis, prognosis, and management.

4.4. Strengths and limitations

The major strength of this study is the derivation of an MPM that can be applied to patients with sepsis at ICU admission to assist clinicians in determining episode-of-care mortality risk. It shows good discrimination, calibration, fit, specificity, and NPV, which is further supported by a bootstrapping procedure. The evaluation of 106 variables ensured an in-depth and thorough approach to determine which variables at ICU admission correlated best to ICU episode-of-care mortality. The CSM-4 is easy to use, with only 10 routinely collected and easily accessible variables, at a relatively inexpensive cost allowing for easier potential future translation into clinical practice and research.

Limitations include using one site and a modest cohort. Furthermore, not all variables were always routinely collected within 4 hours, making analysis of these inadequately powered and limiting the conclusions drawn. The SOFA and qSOFA scores were not able to be accurately estimated for patients on sedatives owing to the retrospective nature of data collection, and these patients were excluded from the assessment of these respective scores. As the focus of this article was model derivation, our model has not been externally validated. Future research should focus on the external validation of the model using a prospective multisite approach, as well as on investigation of ability of the CSM-4 to predict other equally important metrics such as length of stay, morbidity, and post-ICU outcomes.

5. Conclusions

This single-cohort study derived the CSM-4, a sepsis-specific MPM, for use on adults with sepsis at ICU admission. It displays good discrimination, calibration, model fit, specificity, and NPV whilst being easy to use and inexpensive. As a clinical decision support tool, it may assist clinicians with prognostication, risk stratification, shared decision-making, cohort comparison, and the provision of safe and high-quality ICU care. External validation is required.

CRediT authorship contribution statement

Satyen Hargovan: Conceptualisation, Data curation, Formal analysis, Methodology, Project administration, Writing - original draft; **Ronny Gunnarsson**: Conceptualisation, Formal analysis, Methodology, Project administration, Supervision; **Angus Carter**: Conceptualisation, Methodology, Project administration, Supervision; **Alan De Costa**: Conceptualisation, Methodology, Project administration, Supervision; **James Brooks**: Data curation, Writing - review & editing; **Taissa Groch**: Data curation, Writing - review & editing; **Sayonne Sivalingam**: Data curation, Writing - review & editing.

Authors statement

All work on this paper is original. All authors were involved in the submission process and take responsibility for the published piece.

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Conflict of interest

None declared.

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