Supplementary Material

Contents

Supplementary Material

Challenges in the management of septic shock: a narrative review

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Not relevant
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Done in each section
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Not relevant
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Not relevant
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Not relevant
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Not relevant
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Not relevant
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Not relevant
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Not relevant
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Not relevant
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Not relevant
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Not relevant

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Not relevant
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Not relevant
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not relevant
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Not relevant
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Not relevant
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	See each section
Limitations	20	Discuss the limitations of the scoping review process.	See each section
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	See each question
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	See manuscript

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. ;169:467–473. doi: 10.7326/M18-0850

Supplementary Material

Surviving sepsis campaign: research priorities for sepsis and septic shock

Surviving sepsis campaign: research priorities for sepsis and septic shock

Electronic Supplementary Material 1 - Supplemental Table 1

Supplemental Table 1

All questions initially submitted by research committee members

TOPIC 1 - INFECTIONS

1) Nosocomial infections and antibiotic performance. Lower rates of VAP but same with antibiotic prescription? As VAP is the most frequent ICU infection, it can be used as a surrogate for this purpose.
2) Fungal infection in ICU. In the last years Infection guidelines are more and more straightforward for empirical recommending broad (and very expensive) spectrum antifungals in ICU but papers conducted does not totally support change in outcomes
3) Source Control. Weak evidence of SSC recommendations.
4) Recognition of infection / optimal antibiotic therapy (combination? relevance of pkpd? even duration in patients with persisting sepsis)
5) Antibiotic monotherapy versus combination therapy for septic shock
6) Duration of antimicrobial therapy
7) Timing of source control
8) What is the role (if any) of combination antibiotic therapy for septic shock?
9) Evaluate the clinical impact of microbiological rapid diagnostic tests in sepsis. Information regarding RDT are mainly about diagnostic accuracy but information about the clinical impact in terms of escalation, de-escalation, and other outcomes is scarce.
10) We have been having big (sic) discussions within the guidelines group and with the IDSA about the role of combination (versus monotherapy) antibiotics
11) Duration of antibiotic courses
12) double coverage for gram negatives
13) Impact of antimicrobial pharmacokinetic optimization in sepsis and septic shock particularly with respect to continuous/extended infusion of ² -lactams
14) Impact of early empiric combination therapy on outcome of sepsis and septic shock in contrast to other infections without sepsis and organ failure in immunocompetent patients
15) The use of biomarkers and clinical strategies/algorithms to support antimicrobial de-escalation and their impact on outcome in sepsis and septic shock.
16) Antimicrobial management: explore broad versus directed coverage from an epidemiologic standpoint (e.g., does it make sense not to use carbepenems until your cephalosporin resistance rate (or case mortality) crosses a threshold value?)

TOPIC 2 - FLUIDS/RESUSCITATION/HEMODYNAMICS

1) Comparison of fluid type: role of albumin vs crystalloid in <u>early</u> sepsis resuscitation (despite some studies, this question has not yet been answered)
2) Comparison of fluid type: role of normal saline vs. balanced crystalloid solution

(would not advocate as strongly since evidence for deleterious effects of high volume chloride infusion in other areas is not definitive, but septic shock is a good model to test this hypothesis)
3) How much fluid to give – could compare either two different fixed volumes (30cc/kg compared to another fixed volume) or compare targeted volumes (individualized therapy)
4) Do chloride rich or poor crystalloid solutions change outcome in septic shock when significant resuscitation is needed?
5) Evaluate a resuscitation protocol based in dynamic parameters (PLR, VVS, PPV, etc.) on relevant clinical outcomes. The goals are more physiological and discriminate better responders and no-responders but the clinical benefit is not well established.
6) How much volume to give sepsis patient in initial resuscitation
7) Does the initial resuscitation from sepsis-induced hypoperfusion, by using at least 30ml/kg of intravenous crystalloid fluid given within the first 3 hours work in the ward and in the ICU other than in the emergency
8) How septic patients with brain injury or abdominal hypertension should be resuscitated?
9) Is the repeated fluid challenge better than the 30 ml/kg crystalloids bolus resuscitating patients from sepsis?
10) Where do we stand with GDT (is it over or need to be adapted?)
11) Resuscitation endpoints: using venous capacitance/mean systemic pressure as a better surrogate for volume responsiveness or even the elusive "volume status" metric.
12) Vasopressor choice, dosing, and titration schemes. Role of phenylephrine for septic shock (or vasopressin, but that has already been studied, even though questions remain)
13) Is the regional hemodynamics better the systemic to predict sepsis evolution?
14) Recognition and management of new-onset AF in the setting of septic shock (therapy goals, anticoagulation strategies, long-term outcomes).

TOPIC 3 - ADJUNCTIVE THERAPIES (VENTILATION, NUTRITION, ENDOCRINE)
1) Role of lung protective ventilation in sepsis patients *without* ARDS
2) Enteral nutrition support in septic shock
3) Effects of aspects of care we haven't been collecting data on – protocols on vent weaning, sedation, SBTs, ambulation.
4) Timing of metabolic (nutritional) support – does early or late matter?
5) Composition of macronutrient support – sugar, fat, protein – does it matter?
6) Are steroids actually indicated in septic shock? If so, when?
7) Does blockade of co-inhibitors (such as PD1, PDL1, BTLA, CTLA4) improve outcomes in sepsis (not sure if this is a basic science or clinical question)?
8) Does ECMO improve outcomes in ARDS? Does proning? Does paralysis?
9) Evaluation of the different technologies for absortion of mediators: endotoxin absorbers, cytokine absorbers.
10) PK/PD of antibiotics is sepsis + CRRT or Absortion or ECMO or hypoalbuminemia.
11) Volume versus pressure limitation in sepsis induced ARDS
12) Ventilation of patients with sepsis without ARDS
13) Use of esophageal monitors to guide ventilator settings in sepsis induced ARDS
14) The present glucose control guidelines target an upper blood glucose level d 180 mg/dL without a lower target other than hypoglycemia. Future research should identify

whether the upper blood glucose level target should remain d 180 mg/dL or d 150 mg/dL. In addition, a lower target other than hypoglycemia may be more appropriate.
15) In view of the FDA statement "critically ill patients should not be tested with a glucose meter because results may be inaccurate," more accurate glucometers utilizing capillary blood must be developed or a much quicker central laboratory turnaround for results
16) Further study should develop validated, safe, and effective protocols and closed-loop systems for controlling blood glucose concentrations and variability while avoiding hypoglycemia.
17) In the general realm of adjunctive therapies, I think there are many unanswered questions in the realm of nutrition in addition to those you propose regarding management of hyperglycemia. Implementing both of these therapies (management of hyperglycemia, and institution of early nutritional support) generate a substantial body of work for our ICU caregivers, at a time when there are many other competing demands. Despite our recommendations, I think there remain a lot of unanswered or poorly answered questions regarding timing and even utility of early nutritional therapy, as most studies have been carried out in a general critical care cohort, and not specifically in patients with sepsis/septic shock. Moreover, many of the studies have less than optimal methodology and are underpowered. One question that still generates far more smoke than light among my colleagues is when to start enteral nutrition in patients on vasopressor infusions; opinions seem to range all over the map on this one.

TOPIC 4 - SCORING SYSTEM/IDENTIFICATION/SCREENING

<u>Recognition of Sepsis</u>

1) Recognition of sepsis and which would be the best scorings? Differences for Emergency vs Wards. I think that we should better define an immunoscore. Last SEPSIS 3 recommended lactate that is not available in all the places but there is no immunoscore including lymphopenia surprisingly not for predisposition
2) Application of Sepsis-3 criteria to SSC database – does it miss people who are septic? Does it omit people who aren't really septic?
3) Does differentiating severe sepsis/sepsis from septic shock have any effect on process or outcome? That is, does an initial designation of septic shock result in more rapid institution of the bundles? And does that effect mortality/morbidity etc?
4) Is qSOFA (or sepsis-3) or MEWS superior for diagnosing and predicting outcomes in sepsis?
5) Risk stratification in sepsis based in biomarkers
6) Does the qSOFA perform well also in the emergency room?
7) Compare qSOFA prospectively to SIRS as screening tool for sepsis in the ED and hospital floors.
8) Can big data be used to either predict decompensation or predict clinical trajectories in real time in the ICU
9) Use of artificial intelligence or self-learning computing systems for predictive/prognostic scores.

<u>Evaluation of organ dysfunction</u>

1) Building a better SOFA
2) Can we come up with a better marker of organ dysfunction than SOFA?

Diagnosis of infections

1) Improving the sensitivity/specificity of potential point-of-care testing. Possibilities include metabolomics, inflammatory molecules, or RNA sequencing for detection of transcription of virulence factors. Over-arching goal: shorten time to diagnosis. Secondary benefits: improve overall epidemiology and enrollment in clinical trials
2) Isolation of new bacterial, viral, fungal even parasitic pathogens in sepsis and characterization of how these might differ from a bacteria-centric model Main goal: expand diagnosis and therapy to a potential population of sub-clinical patients. Secondary: explore possibilities of multi-pathogen infection. Characterize "normal' versus pathogenic bacteremia

Sepsis Outside the Hospital

1) Routine screening for sepsis in long term care facilities
2) Pre-hospital management of sepsis

TOPIC 5 - ADMINISTRATION/EPIDEMIOLOGY

1) Organizational aspects.
2) Epidemiology of sepsis susceptibility. Main goal: characterize the risk factors (host, pathogen phenotype, response) to tailor therapy, even prophylaxis to specific combinations. Secondary: improve understanding of host-pathogen interactions to look for novel therapeutics.
3) Patient/family values and preferences regarding sepsis – explicitly not addressed in newest guidelines
4) Component analysis of bundles – does fluid matter more than antibiotics? Does anything else matter at all?
5) Evaluate the impact of a secondary evaluation of sepsis treatment at ICU admission. A structured evaluation of the sepsis treatment at ICU admission or after several hours could help to improve antibiotic treatment, source control and hemodynamic resuscitation. Quality improvement intervention.
6) Cost-effectiveness of sepsis interventions.
7) Do quality metrics improve care: Cluster RCT for comparing metrics/bundles to usual care.
8) Risk stratification with biomarker panels

TOPIC 6 - POST-ICU OUTCOMES

1) Long term outcomes in septic patients and economic burden.
2) Incidence of long term sequelae (add some stuff to the database)
3) Effects of institution (timing, use) of bundles on long term sequelae
4) Prevention of organ failure at long term. Analyze the impact of the sepsis treatment on renal or lung function at 1 year.
5) What is the outcome and recovery of the QoL of elderly patients with sepsis?
6) Prognostic/Predictive score at ICU discharge.

TOPIC 7 - BASIC SCIENCE

1) Cellular dysfunction (how to diagnose/ leave it or try to intervene?)
2) What are the mechanisms implicating /triggering recovery?
3) Energy failure research, looking at mitochondrial dysfunction and changes in

metabolism Main goal: enhance diagnosis (lactate: pyruvate ratios may be worth bringing back into the discussion) Secondary: explore organ dysfunction and therapy in terms of energy failure.
4) Therapeutics that could cause phenotypic shifting. Could we turn off virulence?
5) How do we identify patients in the hypo-inflammatory state of sepsis?
6) Does altering the microbiome alter the outcome in sepsis? If so, how do we do it?
7) Identifying the mechanisms by which immune suppression/failure to have an appropriate cellular response lead to poor outcomes in sepsis
8) Pharmacogenomics and precision medicine: identification of specific genotypes that respond or not respond to available treatments like steroids, etc.
9) Does the microbiome influence the sepsis outcome? Understanding the role of lipid mediators (includes resolvins, lipoxins, prostanoids, etc) in sepsis outcomes. This could be broadened to the Lipidome and Metabolome (rather than lipid mediators).
10) How do basic ICU therapies used in humans affect sepsis outcomes? This would include: fluids, sedatives, opioids, transfusions, nutritional supplements, possibly classes of antibiotics
11) Role of non-leukocyte populations in sepsis outcomes (i.e.: neurons, endothelials, etc)
12) Continuing to advance the models to more closely recapitulate the human condition – Multicellular platforms using human cells, continued adaptation of the existing animal models, better defining where mouse models do and do not provide useful pre-clinical information

Surviving sepsis campaign: research priorities for sepsis and septic shock

Electronic Supplementary Material 2 – Supplemental methods

Determination of research questions and priorities:

The structure of the iterative process was determined at a face-to-face meeting at the SCCM annual congress in January 2017. This committee generated a total of 88 questions (supplemental table 1). Many topics proposed by different committee members were nearly identical. These were then grouped into seven topics by the co-chairs based upon the content: infection, fluids and vasoactive agents, adjunctive therapy, administration/epidemiology, scoring/identification, post-intensive care unit, and basic/translational science. When applicable, these were based upon identical subgroups used for the generation of the Surviving Sepsis Campaign guidelines (e.g. infection, adjunctive therapy). However, the guidelines were written exclusively to help guide bedside management, which led many research priorities to fall outside the scope of the guidelines. For questions which did not fit into categories covered within the Surviving Sepsis Campaign guidelines, the co-chairs grouped priorities into broad related topics. Each topic was the responsibility of a subgroup, populated with 3-4 committee members, including a subgroup leader. Each committee member served on multiple subgroups. Teleconferences were then held for each subgroup. The committee co-chairs joined each of these teleconferences. At each teleconference, each submitted question was discussed in detail. Duplicate questions were eliminated, and questions were combined or further refined based upon the discussion. After each teleconference, subgroup members were

independently asked to rank their top three priorities. All questions that received votes were further discussed by the entire committee. Questions that were not listed as being in any subcommittee member's top three priorities were dropped due to the assumption that if no single member of the subcommittee felt strongly about the importance of a question, then the priority of the question could not be that high. Ultimately, this process narrowed the list of research questions to 26 total. After each subcommittee met, the entire committee met by teleconference and then again in person at the ESICM annual congress in September 2017.

Each subcommittee was tasked with drafting their subsection. For each question, a common template was used asking a) what is known, b) what are critiques of current evidence and what are gaps of knowledge and c) directions for future research. While this manuscript generally follows this template, the basic science section was felt to be distinct in which the gaps in knowledge were nearly identical to directions for future research, so these topics were combined. Although every effort was made to make the questions distinct, the more detailed template inevitably led to some overlap between questions. The manuscript was reviewed, revised and then approved by all committee members. Of note, the original intent of the committee was to have this manuscript serve as a broad overview of a research agenda for sepsis with the goal of having more detailed manuscripts from each subgroup in the future.

A. INFECTIONS

1. Should empiric antibiotic combination therapy be used in sepsis or septic shock?

2. Does optimization of antimicrobial pharmacokinetics and pharmacodynamics impact patient outcomes in sepsis?

3. Should antiviral therapy be administered in the context of viral reactivation in patients with acquired immunosuppression?

4. Should rapid diagnostic tests be implemented in clinical practice?

B. FLUIDS AND VASOPRESSORS

1. What are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?

2. What is the optimal fluid for sepsis resuscitation?

3. What is the optimal approach to selection, dose titration, and escalation of vasopressor therapy?

C. ADJUNCTIVE THERAPY

1. Can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?

2. Determine the efficacy of "blood purification" therapies such as endotoxin absorbers, cytokine absorbers and plasmapheresis.

3. What is the ideal method of delivering nutrition support, including route, timing and composition of nutrition support, and whether this varies by hemodynamic status?

4. What is the role of lung protective ventilation in septic patients *without ARDS.*

D. SCORING/IDENTIFICATION

1. What information identifies organ dysfunction?

2. How can we screen for sepsis in varied settings?

3. How can septic shock be identified?

4. What in-hospital clinical information is associated with important outcomes in septic patients?

E. ADMINISTRATION/EPIDEMIOLOGY

1. Which is the optimal model of delivering sepsis care?

2. Which is the epidemiology of sepsis susceptibility and response to treatment?

3. It is possible to stratify the risk of sepsis based on biomarker panels?

F. POST-ICU

1. What is the attributable long-term morbidity and mortality from sepsis?

2. What are the predictors of sepsis long-term morbidity and mortality?

3. Are there potential in-hospital interventions that can impact long term outcomes?

4. Are there potential post-discharge interventions that can improve outcomes?

G. BASIC/TRANSLATIONAL SCIENCE

1. What mechanisms underlie sepsis-induced cellular and sub-cellular dysfunction ?

2. How does sepsis alter bio-energetics and/or metabolism (both enhancement and failure) ?

3. How does sepsis (and/or approaches used to manage sepsis) alter phenotypes and interactions in the host microbiome and do alterations in the microbiome effect outcomes

4. What mechanisms initiate, sustain and terminate recovery ?

Supplementary Material

Health-related outcomes of critically ill patients with and without sepsis

Supplementary Online Content

Thompson K, Taylor C, Jan S, et al. Health related outcomes of critically ill patients with and without sepsis.

Participating sites and investigators from New South Wales, Australia

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eMethods

Expert consensus panel process:

The expert consensus panel was comprised of three intensive care physicians and an intensive care nurse. Decision making regarding baseline variables to be included as matching variables for the propensity score matched analysis was guided by the senior statistician conducting the analysis. Each member of the panel independently reviewed the baseline data collection form for CHEST and documented data points considered risk factors associated with the development of sepsis. After independent consideration of risk factors a consensus group discussion was held to finalize the variables to be included in the matching process. The baseline variables used in the matched analysis are reported in the table below.

Baseline variables used for matching	
Age	Creatinine concentration (μmol/L) before enrolment
Sex (male/female)	Heart rate (beats per minute)
Weight	Mean Arterial Pressure (MAP)
Admission source	Mechanical ventilation prior to enrolment
Medical vs. surgical admission	APACHE II Score
Trauma admission vs. Non-trauma admission	

Baseline variables not used for matching
Traumatic Brain Injury
Glasgow Coma Score
Sedation at time of assessment of eligibility
Neuromuscular blocker at time of assessment of eligibility
Urine output prior to randomisation
Previous receipt and volume of HES
CVP
Lactate
SOFA criteria
APACHE II diagnostic code

Creation of a missing value variable category:

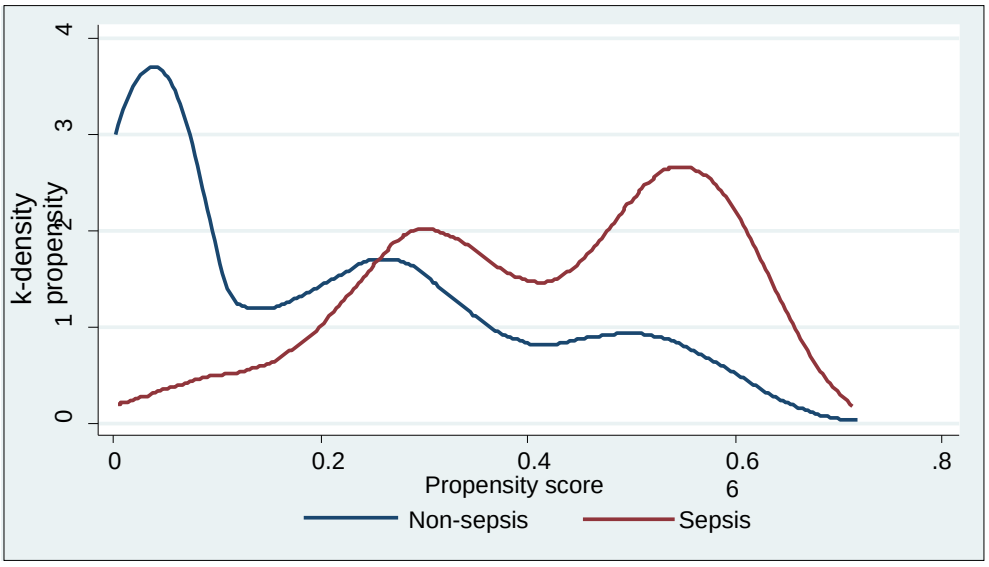
A discussion with the expert consensus panel and the senior statistician occurred to determine potential issues associated with missing data. Continuous variables were categorised to enable higher rates of matching. A plan for handling missing data was developed. After conducting the initial analysis based on the above listed variables, three continuous variables (creatinine concentration, heart rate and mean arterial pressure) had a small amount of data missing (see table below). Where data were missing a separate category for 'missing data' was created for each variable that returned patients with missing data. Patients with missing data remained in the

analysis with propensity scores generated incorporating the 'missing value' variable in cases where data were missing.

Variable	Sepsis patients missing data	Non-sepsis patients missing data
Creatinine concentration (µmol/L) before enrolment	18/806 (2.2)	17/806 (2.1)
Heart rate (beats per minute)	2/806 (0.2)	4/806 (0.4)
Mean Arterial Pressure (MAP)	2/806 (0.2)	2/806 (0.2)

Allocation and distribution of propensity scores:

The range for allocated propensity scores was 0-1, whereby 0 was the lowest possible propensity for sepsis and 1, the highest. After fitting the model for sepsis using the variables specified above, the model gave an AU-ROC of 0.80 indicating a good prediction for sepsis. A calliper threshold of 0.03 was used as a cut-off point for matching i.e. each patient with sepsis had to be matched with a non-sepsis patient whose propensity score was within a calliper of 0.03 units. The distribution of propensity scores for patients with and without sepsis is presented below.



Matching Methods:

The greedy matching method was chosen as the means by which to match patients by propensity score. Using this method a patient with sepsis was randomly selected and the non-sepsis patient whose propensity score was nearest to that of the randomly selected sepsis patient was chosen as the control unit for matching. The process of randomly selecting patients with sepsis and matching to the non-sepsis control was repeated until the number

of patients with sepsis at the time of trial enrolment for whom a match control could be found was exhausted. The process is called greedy matching because the nearest control unit to the randomly selected patient with sepsis is always selected, even if the matched control unit would have served as a closer match than a subsequent randomly selected patient with sepsis.

CHEST Inclusion and Exclusion Criteria

Inclusion:

Written informed consent has been obtained or if not possible, the procedure for obtaining delayed informed consent has been approved by the ethics committee prior to randomisation

Fluid resuscitation is required to increase or maintain intravascular volume that is in addition to maintenance fluids, enteral and parenteral nutrition, blood products and specific replacement fluids to replace ongoing insensible or fluid losses from other sites

The ICU clinician considers that both 6% hydroxyethyl starch (130/0.4) and saline are equally appropriate for the patient and that no specific indication or contraindication for either exists

The requirement for fluid resuscitation must be supported by AT LEAST ONE of the following clinical signs (select all applicable criteria):

- Heart rate > 90 bpm
- Systolic blood pressure (SBP) < 100mmHg **OR** mean arterial pressure (MAP) < 75mmHg **OR** at least 40mmHg decrease in SBP **OR** MAP from the baseline recording
- Central venous pressure < 10mmHg
- Pulmonary artery occlusion pressure < 12 mmHg
- Respiratory variation in systolic or mean arterial blood pressure of >5 mmHg
- Capillary refill time > one second
- Urine output < 0.5 ml/kg for one hour

Exclusion:

The patient has previously received fluid resuscitation prescribed in the ICU during this current ICU admission (this allows inclusion of patients who arrive in the ICU with fluid running)

The patient has received greater than 1000ml hydroxyethyl starch outside the ICU within 24hours prior to randomisation

The patient has a known previous allergic reaction to hydroxyethyl starch solutions

Primary non-traumatic intracranial haemorrhage or severe traumatic intracranial haemorrhage (mass lesion>25ml)

The patient is receiving renal replacement therapy or the ICU physician considers renal replacement therapy is imminent (i.e. renal replacement therapy will start within 6 hrs)

Documented serum creatinine value e 350µmol/L and urine output averaging d 10ml/hr over 12 hours

Documented or clinical suspicion of severe hypernatraemia (Serum Na^+ > 160 mmol/l)

Documented or clinical suspicion of severe hyperchloraemia (Serum Cl^- > 130 mmol/l)

The patient is a woman of child bearing age (18-49 years old), unless evidence of documented menopause, hysterectomy or surgical sterilisation. Unless a negative pregnancy test was done before randomisation OR the patient is breastfeeding

The patient has been admitted to the ICU following cardiac surgery

The patient has been admitted to the ICU for the treatment of burns or following liver transplantation surgery

Death is deemed imminent and inevitable or the patient has an underlying disease process with a life expectancy of <90 days

A limitation of therapy order has been documented restricting implementation of the study protocol or the treating clinician deems aggressive care unsuitable

The patient has previously been enrolled in the CHEST study

The patient has been transferred to the study ICU from another ICU and received fluid resuscitation in that other ICU

eTable 1: Baseline characteristics of matched patients with sepsis and patients with sepsis unable to be matched

	Matched Sepsis (N = 806)	Unmatched Sepsis (N = 99)	p-value
Age	62.5 (16.9)	65.0 (15.6)	0.17
Male	471/806 (58.4%)	63/99 (63.6%)	0.32
Weight	79.7 (23.2)	85.1 (23.4)	0.03
Source of admission to ICU			
Emergency Department	272/ 806 (33.7%)	37/ 99 (37.4%)	0.016
Hospital Floor	231/ 806 (28.7%)	35/ 99 (35.4%)	
Another ICU	11/ 806 (1.4%)	0/ 99 (0.0%)	
Another hospital	129/ 806 (16.0%)	21/ 99 (21.2%)	
Operating room, after emergency surgery	127/ 806 (15.8%)	5/ 99 (5.1%)	
Operating room, after elective surgery	36/ 806 (4.5%)	1/ 99 (1.0%)	
Surgical admission	162/ 806 (20.1%)	0/ 96 (0.0%)	<.0001
Trauma	6/806 (0.7%)	0/99 (0.0%)	0.39
Creatinine (µmol/L)	111.3 (61.4)	152.4 (69.0)	<.0001
Physiological variables			
Heart rate (bpm)	99.5 (22.4)	113.8 (16.6)	<.0001
Mean arterial pressure (mmHg)	73.8 (15.0)	69.1 (14.2)	0.003
Central venous pressure (mmHg)	11.2 (6.0)	11.4 (5.7)	0.81
Lactate (mmol/L)	2.1 (1.6)	3.1 (2.4)	<.0001
Mechanical ventilation	506/ 806 (62.8%)	27/ 90 (30.0%)	<.0001
SOFA scores[b]			
Cardiovascular	1.9 (1.4)	2.1 (1.4)	0.10
Respiratory	2.1 (1.1)	2.0 (1.0)	0.38
Renal	0.7 (0.9)	1.2 (0.9)	<.0001
Hepatic	0.5 (0.8)	0.5 (0.8)	0.31
Haematologic	0.6 (1.1)	0.9 (1.2)	0.006
Total APACHE II[c]	20.0 (7.4)	22.8 (6.0)	0.0003
APACHE II score ≥ 25	209/ 806 (25.9%)	38/ 95 (40.0%)	0.004

Abbreviations: ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

[a] Values are presented as mean ± standard deviation or proportions (percentages).

[b] SOFA scores taken from the 24-hour period prior to trial enrolment. Glasgow Coma Score component of SOFA scores not collected.

[c] APACHE II scores taken from the 24-hour period prior to trial enrolment.

eTable 2: Additional information on ICU admission diagnoses for matched patients

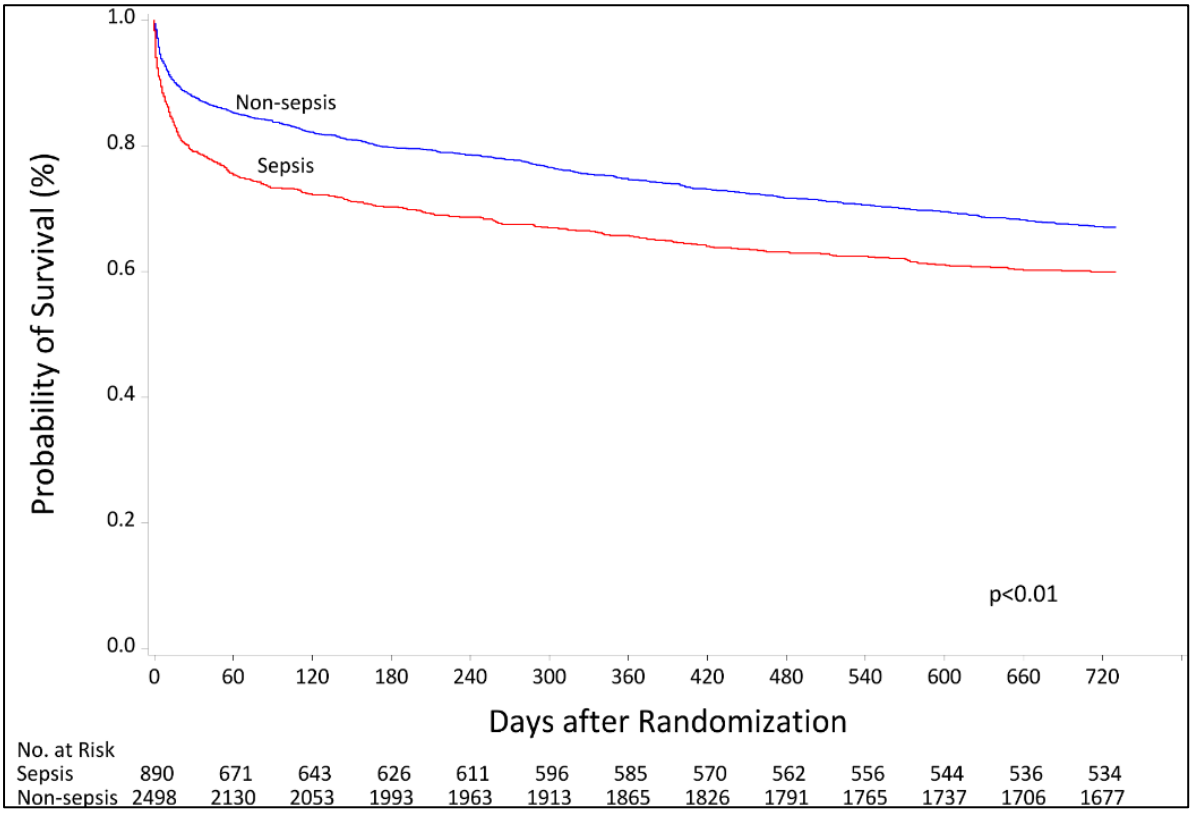
	Sepsis (N = 806)	Non-sepsis (N = 806)	Total (N = 1612)	p-value
Operative admission diagnosis				
Cardiovascular	2/ 162 (1.2%)	17/ 172 (9.9%)	19/ 334 (5.7%)	<.0001
Respiratory	7/ 162 (4.3%)	10/ 172 (5.8%)	17/ 334 (5.1%)	
Gastrointestinal	106/ 162 (65.4%)	102/ 172 (59.3%)	208/ 334 (62.3%)	
Neurological	3/ 162 (1.9%)	7/ 172 (4.1%)	10/ 334 (3.0%)	
Trauma	0/ 162 (0.0%)	3/ 172 (1.7%)	3/ 334 (0.9%)	
Renal	8/ 162 (4.9%)	4/ 172 (2.3%)	12/ 334 (3.6%)	
Gynaecological	0/ 162 (0.0%)	6/ 172 (3.5%)	6/ 334 (1.8%)	
Orthopaedic	19/ 162 (11.7%)	4/ 172 (2.3%)	23/ 334 (6.9%)	
Other post-operative	17/ 162 (10.5%)	19/ 172 (11.0%)	36/ 334 (10.8%)	
Non-operative admission diagnosis				
Cardiovascular	21/ 644 (3.3%)	145/ 634 (22.9%)	166/1278 (13.0%)	<.0001
Respiratory	227/ 644 (35.2%)	171/ 634 (27.0%)	398/1278 (31.1%)	
Gastrointestinal	43/ 644 (6.7%)	95/ 634 (15.0%)	138/1278 (10.8%)	
Neurological	21/ 644 (3.3%)	47/ 634 (7.4%)	68/1278 (5.3%)	
Sepsis	320/ 644 (49.7%)	67/ 634 (10.6%)	387/1278 (30.3%)	
Trauma	1/ 644 (0.2%)	7/ 634 (1.1%)	8/1278 (0.6%)	
Metabolic	11/ 644 (1.7%)	66/ 634 (10.4%)	77/1278 (6.0%)	
Haematological	0/ 644 (0.0%)	6/ 634 (0.9%)	6/1278 (0.5%)	
Renal	0/ 644 (0.0%)	6/ 634 (0.9%)	6/1278 (0.5%)	
Other medical diseases	0/ 644 (0.0%)	24/ 634 (3.8%)	24/1278 (1.9%)	

eTable 3: Health-related Quality-of-Life at six-months (EQ-5D-3L) for the whole surviving CHEST cohort (N=4975)

Characteristics	Sepsis (N = 1320)	Non-sepsis (N = 3655)	Odds ratio	95%CI	p-value
Mobility			0.96	0.85 – 1.10	0.58
No problems	821/1317 (62.3%)	2242/3655 (61.3%)			
Some problems / Unable to walk	499/1317 (37.8%)	1413/3655 (38.6%)			
Self-Care			1.11	0.96 – 1.29	0.16
No problems	1003/1320 (76.0%)	2847/3655 (77.9%)			
Some problems / Unable to wash or dress myself	317/1320 (24.0%)	808/3655 (22.1%)			
Usual activities			0.94	0.83 – 1.07	0.37
No problems	711/1320 (53.9%)	1915/3655 (52.4%)			
Some problems / Unable to perform	609/1320 (46.1%)	1740/3655 (47.6%)			
Pain or Discomfort			0.92	0.81 – 1.04	0.18
No pain or discomfort	739/1320 (56.0%)	1967/3655 (53.8%)			
Some or extreme pain or discomfort	581/1320 (44.0%)	1688/3655 (46.2%)			
Anxiety or Depression			0.97	0.85 – 1.10	0.67
Not anxious or depressed	825/1320 (62.5%)	2258/3655 (61.8%)			
Moderately or extremely anxious or depressed	495/ 1320 (37.5%)	1397/3655 (38.2%)			

eFigure 1: Probability of survival to two-years, unmatched cohort

In the unmatched analysis 534/890 (60.0%) with sepsis and 1677/2498 (67.1%) without sepsis were alive at two years (HR 1.34; 95% CI 1.18-1.52, p<0.01).



eTable 4: Results of sensitivity analyses on survival

Type of Sensitivity Analysis	Subjects	Hazard Ratio	95% CI		p-value
			Lower	Upper	
Unadjusted	all study population (n=3442)	1.35	1.19	1.53	<.0001
Matching method by propensity score	matched study population (n=1612)	1.01	0.86	1.18	0.94
Stratified analysis by quintile of propensity score	subjects with non-missing propensity score (n=3395)	1.06	0.92	1.21	0.44
Inverse probability of treatment weighting (IPTW) using propensity score	subjects with non-missing propensity score (n=3395)	1.01	0.88	1.15	0.94
Adjusted by propensity score as a covariate	subjects with non-missing propensity score (n=3395)	1.05	0.92	1.21	0.47
Adjusted by all covariates which generated a propensity score for sepsis	subjects with non-missing propensity score (n=3395)	1.10	0.96	1.27	0.16

eTable 5: Length of initial ICU and hospital admission, hospital readmissions and costs[a]					
	Unmatched Cohort				
Outcome	**Sepsis (N=905)**	**Non-sepsis (N=2537)**	**Mean difference/ Odds Ratio**	**95% CI**	**p-value**
Length of initial ICU admission (days)	10.0±11.9	7.1±9.1	2.94	2.09-3.79	<.0001
Length of initial hospital admission (days)	22.7±21.6	20.4±19.7	2.29	0.68 – 3.89	0.003
Emergency department visits after discharge [b]	313/713 (43.9)	948/2231 (42.5)	1.06	0.89 – 1.26	0.50
Hospitalizations after discharge[c]	506/706 (71.7)	1597/2220 (71.9)	0.98	0.82 – 1.19	0.89
ICU admissions after discharge[d]	96/705 (13.6)	302/2219 (13.6)	1.00	0.78 – 1.28	0.99
Total ICU costs to 24-months ($A)[e]	47 206±55121	34 142±43 175	13 064	9 094-17 034	<.0001
Hospital costs using AR-DRG to 24-months (A$)	73 516 ±61100	64 676±56 293	8 840	4 291-13 390	0.002

Abbreviations: ICU, intensive care unit; $A, Australian dollars; AR-DRG, Australian Related Diagnostic Group Codes.

[a] Values are presented as mean ± standard deviation or proportions (percentages).

[b] Refers to visits to a public hospital emergency department in New South Wales after discharge from the initial hospital admission.

[c] Refers to public hospitalisations in New South Wales after discharge from the initial hospital admission.

[d] Refers to readmissions to an ICU in New South Wales after discharge from the initial ICU admission.

[e] Total ICU costs derived from multiplying the length of ICU stay by the New South Wales Cost of Care Standard average cost per ICU bed day.

In the unmatched analysis the duration of the initial ICU (10.0±11.9 days vs. 7.1±9.1 days, mean difference 2.94 days, 95%CI 2.09-3.79, p<0.0001) and hospital (22.7±21.6 days vs. 20.4±19.7 days, mean difference 2.29 days, 95% CI 0.68-3.89, p=0.003) admission were longer for patients with sepsis compared to those without sepsis. During the two years after enrolment, similar proportions of patients with and without sepsis had visited an emergency department: 313/713 (43.9%) vs. 948/2213 (42.5%), odds ratio 1.06, 95% CI 0.89-1.26, p=0.50; had been readmitted to hospital 506/706 (71.7%) vs. 1597/2220 (71.9%), odds ratio 0.98, 95%CI 0.0.82-1.19, p=0.89, and readmitted to an ICU, 96/705 (13.6%) vs. 302/2219 (13.6%), odds ratio 1.0, 95% CI 0.78-1.28, p=0.99 respectively. The cost of ICU admissions for patients with sepsis was significantly higher than for patients without

sepsis: A$47,206±55,121 vs. A$34,142±43,175, mean difference A$13 064, 95%CI A$9,094-$17,034, p=<0.0001. The overall cost of hospital treatment to two years was significantly higher in patients with sepsis: A$73,516±61,100 vs. A$64,676±56,293, mean difference A$8,840, 95%CI A$4,291-$13,390, p=0.002.

eTable 6: Patient characteristics at baseline Sepsis-3 definition[a]

	Sepsis SOFA ≥2 (N = 760)	Non-sepsis SOFA ≥ 2 (N = 760)	p-value
Age	63.5±16.6	63.8±16.4	0.74
Male	458 (60.3)	461 (60.7)	0.87
Weight	80.8±24.1	80.4±22.9	0.78
Source of admission to ICU			
Emergency Department	257 (33.8)	248 (32.6)	0.99
Hospital Floor	210 (27.6)	212 (27.9)	
Another ICU	11 (1.4)	10 (1.3)	
Another hospital	126 (16.6)	132 (17.4)	
Operating room, after emergency surgery	123 (16.2)	125 (16.4)	
Operating room, after elective surgery	33 (4.3)	33 (4.3)	
Surgical admission	148 (19.5)	150 (19.7)	0.90
Trauma	6 (0.8)	2 (0.3)	0.16
Physiological variables			
Heart rate (bpm)	99.5±22.2	95.3±24.1	0.0004
Mean arterial pressure (mmHg)	73.6±15.0	74.1±15.9	0.53
Central venous pressure (mmHg)	11.6±6.0	11.1±5.3	0.40
Lactate (mmol/L)	2.1±1.6	2.4±2.2	0.06
Creatinine (µmol/L)	115.4±62.3	113.6±65.4	0.58
Mechanical ventilation	497 (65.4)	497 (65.4)	1.0
SOFA scores[b]			
Cardiovascular	2.0±1.4	1.8±1.4	0.002
Respiratory	2.2±1.0	2.1±1.1	0.01
Renal	0.8±0.9	0.7±0.9	0.30
Hepatic	0.5±0.8	0.4±0.8	0.19
Haematologic	0.6 ±1.1	0.5±0.9	0.01
Total APACHE II [c]	20.5±7.3	20.6±7.9	0.89
APACHE II score 25	213 (28.0)	218 (28.7)	0.78

Abbreviations: ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

[a] Values are presented as mean ± standard deviation or proportions (percentages)

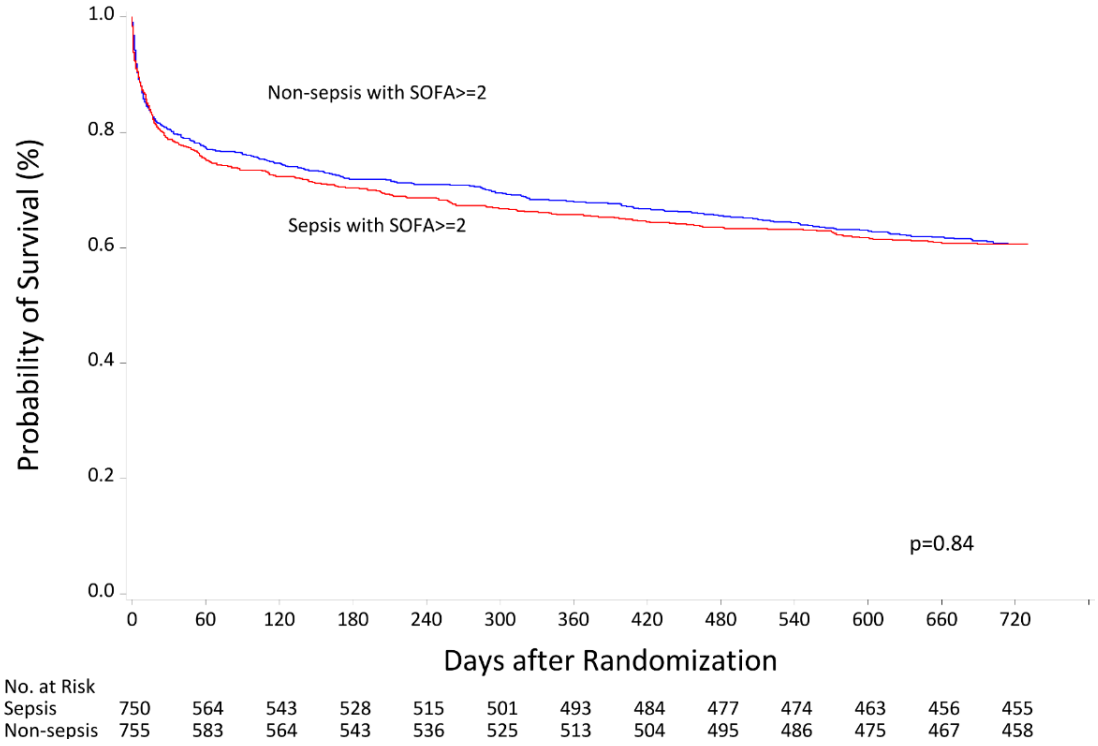
[b] SOFA scores taken from the 24-hour period prior to trial enrolment. Glasgow Coma Score component of SOFA scores not collected.

[c] APACHE II scores taken from the 24-hour period prior to trial enrolment.

eTable 7: Health-related Quality-of-Life at six-months (EQ-5D-3L)					
Characteristics	**Sepsis SOFA ≥ 2 (N = 507)**	**Non-sepsis SOFA ≥ 2 (N = 516)**	**Odds Ratio**	**95%CI**	**p-value**
Mobility			0.98	0.76-1.26	0.98
No problems	309/ 506 (61.1%)	312/ 515 (60.6%)			
Some problems / Unable to walk	197/ 506 (38.9%)	203/ 515 (39.4%)			
Self-Care			0.99	0.75-1.30	0.91
No problems	372/ 506 (73.5%)	378/ 516 (73.3%)			
Some problems / Unable to wash or dress myself	134/ 506 (26.5%)	138/ 516 (26.7%)			
Usual activities			0.97	0.76-1.24	0.53
No problems	273/ 506 (54.0%)	274/ 516 (53.1%)			
Some problems / Unable to perform	233/ 506 (46.0%)	242/ 516 (46.9%)			
Pain or Discomfort			0.96	0.75-1.23	0.80
No pain or discomfort	291/ 507 (57.4%)	291/ 516 (56.4%)			
Some or extreme pain or discomfort	216/507 (42.6%)	225/ 516 (43.6%)			
Anxiety or Depression			0.77	0.60-0.99	0.12
Not anxious or depressed	328/ 506 (64.8%)	301/ 514 (58.6%)			
Moderately or extremely anxious or depressed	178/ 506 (35.2%)	213/ 514 (41.5%)			

eFigure 2: Probability of survival to two-years patients with Sepsis-3 vs non-sepsis patients with SOFA≥2:

HR=1.02, 95%CI 0.87-1.19, P-value=0.84



No. at Risk													
Sepsis	750	564	543	528	515	501	493	484	477	474	463	456	455
Non-sepsis	755	583	564	543	536	525	513	504	495	486	475	467	458

eTable 8: Length of ICU and hospital stay, readmissions, costs patients with Sepsis-3 vs non-sepsis patients with SOFA≥2

Outcomes	Sepsis SOFA ≥ 2 (N=760)	Non Sepsis SOFA ≥ 2 (N=760)	Mean difference/ Odds Ratio	95%CI	p-value
Length of initial ICU admission (days)	10.5±12.4	8.1±10.2	2.40	1.26 – 3.55	<0.001
Length of initial hospital admission (days)	23.2±21.9)	19.3±19.2	3.91	1.83 – 5.99	<0.001
Emergency department visits after discharge [b]	258/598 (43.1)	281/618 (45.5)	0.91	0.73 – 1.14	0.41
Hospitalizations after discharge[c]	421/ 589 (71.5)	446/610 (73.1)	0.92	0.72 – 1.19	0.53
ICU admissions after discharge[d]	80/589 (13.6)	114/609 (18.7)	0.68	0.50 – 0.93	0.68
Total ICU costs to 24-months ($A)[e]	49 131±57 700	39 031±48327	10 100	4743 – 15457	<0.001
Hospital costs using AR-DRG to 24-months (A$)	111 543±137482	94 324±106337	10 017	3888 - 16147	0.006

Abbreviations: ICU, intensive care unit; $A, Australian dollars; AR-DRG, Australian Related Diagnostic Group Codes.

[a] Values are presented as mean ± standard deviation or proportions (percentages)

[b] Refers to visits to a public hospital emergency department in New South Wales after discharge from the initial hospital admission

[c] Refers to public hospitalisations in New South Wales after discharge from the initial hospital admission

[d] Refers to readmissions to an ICU in New South Wales after discharge from the initial ICU admission

[e] Total ICU costs derived from multiplying the length of ICU stay by the New South Wales Cost of Care Standard average cost per ICU bed day