**Prevalence, causes, management, and outcomes of sepsis**

**in Asia’s intensive care units**

The MOSAICS II Study

(Management of Sepsis in Asia’s Intensive Care unitS)

Asian Critical Care Clinical Trials Group

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**STUDY PROTOCOL**

1. **Abstract**

The latest definition of sepsis, Sepsis-3, was derived from databases in high-income countries in the West. However, little is known about the epidemiology of sepsis in much of the rest of the world.

The primary objective of this study is to determine the prevalence of sepsis defined by the Sepsis-3 guidelines as a reason for intensive care unit (ICU) admission in Asia, as well as its causes and outcomes. Secondary objectives are to evaluate the time to management of sepsis with a focus on recommendations by the Surviving Sepsis Campaign guidelines; to compare the epidemiology and management of sepsis in Asian ICUs in high, middle, and low-income countries and regions; and to study the prevalence and outcomes of sepsis as a result of specific infections.

National coordinators will invite ICUs in their respective countries and regions to participate in this cross-sectional point-prevalence observational study using a mix of sampling frames aimed at maximising representativeness. All adult ICUs other than predominantly neurosurgical, coronary, and cardiothoracic ones are eligible for participation. All patients admitted with sepsis who are in these ICUs on four study days chosen to represent the four seasons in 2018/9 will be included. Patient-level data collected will include demographics; comorbidities; type and source of admission; severity scores; site of infection; culture, serological, molecular, and histological tests for diagnosis of various bacterial, parasitic, viral, fungal and zoonotic infections; life-sustaining treatments and source control; time to obtaining blood cultures, antibiotic administration, lactate measurement, and fluid boluses; and hospital and ICU mortality and length of stay. ICU-level data collected will include the total number of patients (including those without sepsis) in the ICUs on the study days, and the type, capacity, and capabilities of the ICUs.

Findings from this study in the world’s largest continent will shed much needed light on the epidemiology of sepsis both in high-income countries and in low and middle-income countries, and potentially lead to programmes to improve its management and ultimately its outcomes.

1. **Background**

The latest definition of sepsis, Sepsis-3, requires patients to have life-threatening organ dysfunction (an increase of Sequential Organ Failure Assessment Score [SOFA] score > 2 from baseline) caused by a dysregulated host response to infection.[1](#_ENREF_1) This definition was derived from and validated through databases in the United States (except for one hospital in Germany).2 Compared with other well-established definitions such as the systemic inflammatory response syndrome (SIRS), SOFA was shown to be a better predictor of mortality. In addition, the abbreviated quick SOFA (qSOFA) score emerged as a new measure for the prediction of poor outcomes among patients with infection. Whether this is generalizable to the rest of the world remains unclear.

Meanwhile, Fleischmann and colleagues, on behalf of the International Forum of Acute Care Trialists (InFACT), performed a systematic review to estimate the worldwide incidence and mortality of sepsis. Strikingly, only 13% of the world’s countries were represented in the review, as population-level epidemiologic data for sepsis were close to non-existent for low and middle-income countries.[3](#_ENREF_2) Yet, the Global Burden of Disease Study 2015 found that while they did not feature significantly in high-income countries, diarrheal diseases such as cholera and Salmonella infections, human immunodeficiency virus (HIV) infections, and tropical diseases such as malaria and dengue fever were among the main causes of death in low-income countries.4

There thus exists a current disconnect between the way sepsis is perceived and defined in high-income countries and in low and middle-income countries.5 To illustrate, in the Extended Prevalence of Infection in Intensive Care (EPIC II) study, 51% of patients in the participating 1265 intensive care units (ICUs) from 75 countries were considered infected on the day of the study in the year 2007.6 Surprisingly, parasites accounted for only 0.7% of all defined infections (0% in Africa and 0.6% in Asia), and there was no specific mention of cholera, Salmonella infections, and viral infections.

Asia is the world’s largest continent and is home to approximately 60% of the world’s population. Estimates – based predominantly on extrapolations from the West – that Asia accounts for at least half of the cases of sepsis in the world are thus not unexpected.7 Asia has a mix of high, middle, and low-income countries, and it is likely that the causes and outcomes of sepsis in these countries will vary significantly.8

The management of sepsis also varies across Asia. The Management Of Severe sepsis in Asia’s Intensive Care unitS (MOSAICS) study showed compliance rates to the Surviving Sepsis Campaign’s resuscitation bundles of only 2.3%, 6.9%, and 10.0% in low-income, middle-income, and high-income countries and regions respectively (compared to 19% in Europe and North America).9 Meanwhile, the management of sepsis has evolved over the last decade. Rather than early goal-directed therapy guided by central venous pressure and central venous oxygen saturation10, the Surviving Sepsis Campaign’s 3-hour bundle now focuses on blood cultures, early antibiotics, lactate measurement, and adequate fluid resuscitation.11-15

Given the significant changes in the recommended definitions and management of sepsis despite the paucity of data on this life-threatening condition in much of the world, a re-examination of sepsis in this era of Sepsis-3 is timely. The Asian Critical Care Clinical Trials (ACCCT) Group has a good track record of multinational and multi-centre research in Asia and is well poised to do this.

1. **Objectives of the study**

 **Primary objective of the main study**

To determine the prevalence of sepsis defined by the Sepsis-3 guidelines as a reason for ICU admission in Asia, as well as its causes and outcomes.

**Secondary objectives of the main study**

1. To evaluate the time to management of sepsis with a focus on recommendations by the Surviving Sepsis Campaign guidelines: blood cultures, antibiotics, lactate measurement, and fluid resuscitation.
2. To compare the prevalence, causes, outcomes, and management of sepsis in Asian ICUs in high, middle, and low-income countries and regions, defined according to the World Bank classification.
3. To specifically study the prevalence and outcomes of sepsis as a result of malaria, dengue, tuberculosis, cholera, and Salmonella infections, as well as culture-negative sepsis.
4. **Study ICUs**

An ICU is any unit capable of providing invasive mechanical ventilation and organ support, such as using vasoactive medications and renal replacement therapy, and recognised to be an ICU by its hospital.16

**Inclusion criteria**

1. Adult ICUs.

**Exclusion criteria**

1. Predominantly paediatric ICUs.
2. Predominantly neurosurgical ICUs.
3. Predominantly coronary and cardiothoracic ICUs.
4. **Study patients**

**Inclusion criteria**

1. All adult patients who are admitted to the participating ICUs from 0000 Hr (midnight) to 2359 Hr (midnight) of the day of data collection for sepsis.They can be patients admitted from the emergency departments, or transferred from anywhere in the same hospital or other hospitals or elsewhere.
2. All adult patients who were admitted for sepsis to the participating ICUs prior to the day of data collection and who are still in the participating ICUs on the day of data collection.



*Figure 1:* Illustration of study patients to be included in the study

The definition of sepsis is based on an increase of SOFA score > 2 from baseline. For patients with no prior organ dysfunction, the baseline SOFA score is assumed to be zero.1

**Exclusion criteria**

1. Patients younger than 18 years old.
2. Neurosurgical patients, defined as patients who are admitted to the ICU after or pending neurosurgical interventions.
3. Cardiac patients, defined as patients who are admitted to the ICU after cardiac surgery, for acute myocardial infarction without shock or respiratory failure, and for arrhythmias.
4. **Conduct of the study**

This is a cross-sectional, point prevalence observational, multi-centre study where patients are enrolled on 4 separate days to represent the different seasons of the year. These days will be decided at a later date before the study commences. The study will be conducted over a year (2018/2019).

On the study days, data collection will commence for all study patients in the participating ICUs via online case report forms. Details of the forms are provided in the next sections. First, data will be collected for all patients admitted with sepsis. There will also be a focus on time to blood cultures, antibiotics, lactate measurement, and fluid resuscitation. Second, each participating ICU will complete another online questionnaire detailing the type, capacity, and capabilities of the ICU prior to the commencement of the study.

Management of the patients will be left completely to the managing physicians. The study protocol does not dictate the performance of specific investigations. Thus, only variables as part of usual care will be recorded.

1. **Data collection**

Standardized online case report forms will be used. When online access is unavailable, hard copy forms will be used. The form is self-explanatory. Refer to *Appendix 1* for further details. The data variables collected should be based on the results at the time of admission to the ICU. Admission is defined as the earliest documented time that a patient is physically in a bed in the ICU. Variables to be recorded for each patient include the following:

1. Date of hospital admission and date and time of ICU admission.
2. Demographics: Age, gender.

c. Comorbidities. Refer to Table 1 below for definition of the comorbidities.

|  |  |
| --- | --- |
| **Comorbidity** | **Definition** |
| Cardiovascular disease | Ischaemic heart disease (IHD), heart failure |
| Chronic lung disease | Chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, post-tuberculosis related lung disease, interstitial lung disease (ILD), excluding primary or secondary lung malignancy. Patients who are undergoing treatment for tuberculosis or non-tuberculosis mycobacterium (NTM) prior to ICU admission should be included in this category |
| Chronic neurological disease | Strokes, neuromuscular disease, epilepsy, movement disorders, excluding brain tumors |
| Chronic kidney disease | Kidney damage > 3 months (abnormal blood/urine composition or radiological renal abnormalities or glomerular filtration rate < 60mL/min/1.73m2), excluding renal cell carcinoma |
| Peptic ulcer disease | Gastric and duodenal ulcers |
| Chronic liver disease | Prolonged course of hepatic disease > 6 months, excluding hepatocellular cancer |
| Diabetes mellitus | Any type of diabetes mellitus |
| Human immunodeficiency virus (HIV) infection | Positive HIV serology with or without acquired immunodeficiency syndrome (AIDS)-defining illness |
| Connective tissue disease | Presence of appropriate clinical symptoms and high titres of specific autoantibodies that fulfill the criteria of different connective tissue diseases. Examples include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), gout, systemic sclerosis, scleroderma |
| Immunosuppression | Patients on long term steroids or other immunosuppressants (excluding patients with haematological conditions or other malignancies) |
| Haematological malignancies | Include leukaemia, lymphoma, multiple myeloma |
| Solid malignant tumours | Such as breast, colon, lung, prostate, skin, etc |

*Table 1*: Definitions of comorbidities

d. Type of admission. Options include medical, elective surgical or unscheduled surgical admissions.

e. Source of admission. Options include emergency department, operating room, general wards, other ICUs or high-dependency units, inter-hospital transfer, and others.

1. Determination of severity. Guidance will be provided on the calculation of the SOFA, qSOFA, systemic inflammatory response syndrome (SIRS) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores.17
2. Parameters required are as follows:
	1. Vital signs (upon admission to the ICU)
		* Mean blood or arterial pressure (MAP), systolic blood pressure (SBP), heart rate (HR)
		* Respiratory rate (RR)
		* Temperature (degrees Celsius)
		* Glasgow Coma Scale (GCS)
	2. Blood investigations (record those that are obtained within the first 24 hours of ICU admission. The results closest to the time of ICU admission should be the ones recorded. If no such investigations are available within the 1st 24 hours of ICU admission, record the results which are obtained within 4 hours prior to ICU admission, with preference being given to those closest to the time of ICU admission:
		* White cell count (x109/L), platelets (x109/L), haemoglobin (g/dL), haematocrit (%)
		* Sodium (mmol/L), potassium (mmol/L), creatinine (mmol/L)
		* Bilirubin (umol/L)
		* pH, PaO2 (mmHg)
		* FiO2. Refer to Table 2 for corresponding values of FiO2. This is adapted from the oxygen conversion table in the EPIC II study.6, 18 The PaO2/FiO2 ratio will be calculated.

|  |  |
| --- | --- |
| **Oxygen tank flow rate in liters/min** | **FiO2** |
| Nasal cannula  |
| 0 L/min | 21 |
| 1 L/min | 24 |
| 2 L/min | 28 |
| 3 L/min | 32 |
| 4 L/min | 36 |
| 5 L/min | 40 |
| 6 L/min | 44 |
| Face mask |
| 5 L/min | 40 |
| 6 L/min | 50 |
| 7-8 L/min | 60 |
| Nasopharyngeal catheter |
| 4 L/min | 40 |
| 5 L/min | 50 |
| 6 L/min | 60 |
| Venturi mask | FiO2 as set on the apparatus |
| Face mask with reservoir |
| 6 L/min | 60 |
| 7 L/min | 70 |
| 8 L/min | 80 |
| 9 L/min | 90 |
| 10 L/min | 95 |
| 15 L/min (non-rebreather mask) | 100 |
| High flow nasal cannula, non-invasive ventilation, mechanical ventilation |
| Regardless of inspiratory flow, positive end-expiratory pressure (PEEP) | FiO2 as set on the apparatus |

*Table 2*: Corresponding fraction of inspired oxygen (FiO2) to the level of oxygen supplementation5

1. Sites of infection.19-20 Options include respiratory, urinary tract, abdominal (apart from urinary tract), neurological, bone or joints, skin or cutaneous sites, intravascular catheter, infective endocarditis, primary bacteraemia or systemic. Brief descriptions of infections include but are not limited to:

i. Pneumonia requires the presence of radiographic infiltrates and features including fever or hypothermia, leukocytosis or leukopenia and purulent respiratory secretions. Positive cultures are defined in Table 3.

ii. Intra-abdominal infections include but are not limited to intra-abdominal abscesses, peritonitis, biliary tract infections, pancreatic infections, enteritis, and colitis.

1. Urinary tract infection requires typical features of fever, urgency, frequency, dysuria, pyuria and haematuria, together with confirmatory radiological features and/or positive culture results as defined in Table 3.
2. Soft tissue and skin infections include surgical site infections, septic arthritis, cellulitis and necrotizing fasciitis.
3. Catheter-related blood stream infection is defined as bacteremia with an intravascular device in situ and no other apparent source for the bloodstream infection, with culture results as defined in Table 3.
4. Systemic infections refer to infections without a clear primary site of infection, as is often the case in infections such as dengue and malaria.
5. Positive culture result. This is defined as the presence of any aetiologic agents recovered from any of the following mediums. To ensure that any microorganisms isolated are the cause of infection that resulted in ICU admission, only results of cultures collected within the two days before and the two days after admission, unless they are deemed to be colonizers or contaminants by the managing physicians, should be recorded. Microorganisms isolated more than two days before ICU admission may be recorded if they are judged to have led to the clinical deterioration by the managing physicians. Refer to Table 3 for the various mediums tested and Table 4 for the list of aetiologic agents.16, 20

|  |  |
| --- | --- |
| **Medium** | **Definition of positive culture result** |
| Blood | * Microorganism cultured
* Common skin contaminants like coagulase-negative staphylococci, *Bacillus* species, *Corynebacterium*, species, micrococci and *Propionibacterium* species are disregarded unless they are deemed significant by the managing physician or cultured from > 2 blood cultures
* Primary bacteraemia is diagnosed if the microorganism cultured is not related to any infected site
* For catheter-related bloodstream infection, paired blood cultures must yield microbiological diagnosis21-22
	+ Catheter blood culture yielding 5-fold higher yield than peripheral blood culture
	+ Catheter blood cultures positive > 2 hours earlier than peripheral blood culture
 |
| Sputum, blind endotracheal aspirates, bronchoalveolar lavage (BAL) | * Microorganism cultured
* Moderate to heavy growths of bacteria with few epithelial cells seen on gram stain examination (< 10 per high power field)
* *Candida* is often a contaminant in immunocompetent patients.23 Do not record *candida* as the aetiology of pneumonia unless the managing physician determines otherwise
 |
| Pleural fluid | * Microorganism cultured
* Pus
 |
| Urine | * Isolation of 105 colony forming units (cfu)/mL of microorganisms (or 103 cfu/mL in catheterized patients)
 |
| Stool | * Microorganism cultured
 |
| Bile, peritoneal fluid | * Microorganism cultured
 |
| Liver abscess fluid | * Microorganism cultured
 |
| Non-liver abscess fluid | * Microorganism cultured
 |
| Cerebrospinal fluid | * Microorganism cultured
 |
| Synovial fluid | * Microorganism cultured
 |
| Soft tissue, wound and skin cultures, surgical site cultures | * Microorganism cultured
 |

 *Table 3*: Definition of positive cultures

|  |  |  |
| --- | --- | --- |
| **Gram-positive** | **Gram-negative** | **Fungal** |
| Methicillin-sensitive *Staphylococcus aureus* | *Klebsiella pneumoniae* | *Candida albicans* |
| Methicillin-resistant *Staphylococcus aureus* | *Escherichia coli* | *Candida* non-albicans |
| *Streptococcus pneumoniae* | *Pseudomonas aeruginosa* | *Aspergillus* species |
| Other *Streptococcus* species | *Acinetobacter baumannii* | Others |
| *Enterococcus* | *Bulkholderia pseudomallei* |  |
| Others | *Enterobacter cloacae* |  |
|  | *Haemophilus influenza* |  |
|  | *Salmonella* species |  |
|  | *Citrobacter* species |  |
|  | *Stenotrophomonas maltophilia* |  |
|  | *Proteus* species |  |
|  | *Bacteroides fragilis* |  |
|  | Others |  |

*Table 4:* List of aetiologic agents that can potentially be recovered from cultures

1. Other serological, molecular, culture and histological tests required for diagnosis of various bacterial, parasitic, viral, fungal and zoonotic infections. Refer to Table 5 for further details.5, 24

|  |  |
| --- | --- |
| **Pathogen** | **Test results** |
| Bacteria |
| Tetanus | Nil. Clinical diagnosis25 |
| Tuberculosis | Positive culture from any medium, histological diagnosis,26 polymerase chain reaction (PCR) tests |
| Non-tuberculous mycobacteria | Positive culture from any medium, histological diagnosis |
| Fungi (apart from fungal cultures) |
| Aspergillosis | BAL galactomannan > 1.027-28 |
| Blastomycocis | Antigen testing (serum) |
| Histoplasmosis | Antigen testing (urine or serum) |
| Cryptococcus | Antigen testing (serum) |
| Parasites |
| Malaria | Thick and thin blood films, rapid diagnostic tests (serum)29 |
| Virus |
| Measles | Serum serology (presence of IgM), PCR tests |
| Chikungunya | Serum or CSF serology (presence of IgM), PCR tests30 |
| Dengue | Serum antigen, serology (presence of IgM), PCR tests31 |
| Influenza  | PCR tests, immunofluorescence assays from BAL, endotracheal aspirate, nasopharyngeal swabs, nasal swabs, throat swabs32 |
| Other respiratory viruses apart from influenza | PCR tests, immunofluorescence assays from BAL, endotracheal aspirate, nasopharyngeal swabs, nasal swabs, throat swabs33 |
| Rabies | PCR tests34 |
| Zoonoses |
| Leptospirosis | Serum serology (presence of IgM) |
| Q fever | Serum serology (presence of IgM) |
| Rickettsia | Serum or eschar serology (presence of IgM)35-36 |

*Table 5*: Other tests for diagnosis of various parasitic, viral, fungal and zoonotic infections

1. Options will be provided for clinical diagnoses made and persisted with due to strong clinical suspicion:
2. Even though specific cultures, serologies, molecular, and/or histological tests were performed and negative.
3. Because specific cultures, serologies, molecular, and/or histological tests are not available in the ICU.
4. Treatment in ICU
5. Use of vasopressors/inotropes.
6. Invasive mechanical ventilation (MV). Invasive MV is done through a laryngeal mask, an endotracheal, endobronchial or tracheostomy tube in place. Invasive MV does not include the use of mask/hood non-invasive ventilation (NIV). Duration of MV is measured from the time of starting invasive MV until the time of successful extubation or breathing on a tracheostomy mask (with no need for a return to MV for ≥ 48 hours), whichever comes first.
7. Noninvasive ventilation (NIV). NIV is the use of continuous positive airway pressure (CPAP) or noninvasive positive pressure ventilation (NIPPV) only. Duration of NIV is measured from the time of starting NIV until the time of successful cessation of NIV (with no need for a return to MV for > 48 hours) or subsequent intubation, whichever comes first. This does not include NIV use peri-intubation or extubation.
8. High flow nasal cannula (HFNC). Duration of HFNC is measured from the time of starting HFNC until the time of successful cessation of HFNC (with no need for a return to HFNC for > 48 hours), switch to NIV or subsequent intubation, whichever comes first. This does not include HFNC use peri-intubation or extubation.
9. Renal replacement therapy (RRT). This refers to any patient requiring intermittent haemodialysis (IHD), peritoneal dialysis (PD), sustained low efficiency dialysis (SLED) or continuous renal replacement therapy (CRRT).
10. Transfusion. This refers to the delivery of blood products to the patient. These include red blood cells, platelets and fresh frozen plasma.
11. Source control. The timing at which source control measures are first implemented will be collected.
	* + Procedures that do not require surgical intervention, e.g. removal of infected intravascular or other catheters, insertion of ascitic drains, pleural drains, percutaneous drains for liver abscesses
		+ Surgical intervention, e.g. debridement of infected necrotic tissue
12. Limitation of life-sustaining treatments at any time during the current ICU stay (does not include orders before or after current ICU stay), even if any limitation orders are subsequently revoked.
13. Do-not-resuscitate (DNR) order.37 This refers to an order to withhold cardiopulmonary resuscitation (CPR) in the event of cardiopulmonary arrest. Any DNR order should be recorded, regardless of whether or not cardiopulmonary arrest occurs.
14. Withdrawal of life-sustaining treatments. This refers to the cessation of otherwise clinically indicated vasopressors/inotropes, invasive mechanical ventilation, renal replacement therapy, antibiotics, enteral/parenteral nutrition, intravenous hydration, and/or blood products.38-39 Withholding refers to an order not to start any vasopressor or inotrope even if otherwise clinically indicated.37
15. Withholding of life-sustaining treatments. This refers to an order made (pre-emptively or at the time of deterioration) not to start or escalate any of the above-stated life-sustaining treatments even if otherwise clinically indicated at the time of the decision.37
16. Note that DNR orders are considered separately from withdrawal and withholding of life-sustaining treatments. In addition, withdrawal and withholding are considered mutually exclusive, i.e. once the option of withdrawal has been chosen in the questionnaire, withholding should not be chosen.
17. **Surviving Sepsis Campaign bundle**
18. The online case report forms as detailed in *Appendix 1* will also require additional details on the Surviving Sepsis Campaign’s 3-hour bundle.11 This consists of blood culture collection prior to antibiotic administration, antibiotic administration, lactate measurement, and fluid resuscitation. Time zero is the onset of sepsis. This is determined according to the patient’s location within the hospital when sepsis is diagnosed:

i. For patients presenting to the emergency department with sepsis, time zero is defined as the time of triage.

ii. For patients who develop sepsis in the wards or other non-emergency department units, time zero is determined by searching the clinical documentation for the time of diagnosis of sepsis. This may include, for example, a physician’s note or timed and dated orders, a timed and dated note of a nurse’s discussion of sepsis with a physician, or timed records initiating referral to the ICU for sepsis.

* 1. If no time and date can be found by searching the chart, the default time of presentation is the time of admission to the ICU.
	2. In the rare event that the patient does not present with sepsis in the emergency department, but deteriorates and develops sepsis in the emergency department while being observed or while waiting for a hospital bed, time zero is determined by searching the clinical documentation for the time of diagnosis of sepsis. This may include, for example, a physician’s note or timed and dated orders, a timed and dated note of a nurse’s discussion of sepsis with a physician, or timed records initiating referral to the ICU for sepsis.
1. The time of completion of the various components of the 3-hour bundle will be recorded. In cases where targets are achieved in the 1 hour before time zero, the latter time will be recorded (this will be translated to a time of 0 minutes from time zero during data analysis).

i. Time of obtaining blood cultures.

ii. Time of antibiotic administration.

1. Time of lactate measurement.
2. Amount of fluid bolus administered within the first 3 hours from time zero (recorded in mLs).
3. The need for a fluid bolus will be assessed by:

i. The presence of any episode of hypotension (SBP < 90 mmHg or MAP < 65 mmHg) between time zero and in the 3 hours thereafter.

ii. Any lactate measurement > 2 mmol/L between time zero and the 3 hours thereafter.

1. **Follow up and outcomes**

All patients will be followed up till one of the following occurs, whichever is later:

1. Discharge from the current hospital admission.
2. Death during the current hospital admission (either in ICU or after discharge from ICU).

Outcomes to be collected:

1. All-cause in-hospital mortality
2. All-cause ICU mortality.
3. Length of ICU stay.
4. Length of total hospital stay.
5. **Data collection at the individual ICU level**
	1. The total number of patients in the ICU on the day of data collection, regardless of diagnosis and the presence or absence of sepsis will be recorded. This is defined as the total number of patients that are in the ICU on the chosen day of data collection from 0001 Hr to 2359 Hr (Day 1).

i. This includes:

* + - Patients admitted to the ICU before Day 1 and are still in the ICU on Day 1
		- Patients admitted to the ICU on Day 1 and die or are discharged on the same day
		- Patients admitted to the ICU on Day 1 and then stay beyond Day 1

ii. This excludes (as stated in paragraph 4):

* + - Neurosurgical patients, defined as patients who are admitted to the ICU after or pending neurosurgical interventions
		- Cardiac patients, defined as patients who are admitted to the ICU after cardiac surgery, for acute myocardial infarction without shock or respiratory failure, and for arrhythmias

(These patients are excluded regardless of the type of ICUs they are in for the sake of consistency, since predominantly neurosurgical, coronary, and cardiothoracic ICUs are excluded from this study.)

* 1. Participating ICU directors will also fill up an additional questionnaire on the type, capacity, and capabilities of ICU. Refer to *Appendix 2* for further details. Several definitions include:

i. A closed ICU is defined as one in which the patient care is directed by the intensivist and the ICU team. Only the ICU team doctors can write the orders.

ii. An intensivist is defined as a physician who has passed the intensive care certification examinations or who has completed training in an accredited intensive care fellowship or who treats the total patient and not a single organ system and is recognized by his or her institution as an intensivist.

1. A rural hospital is defined as non-metropolitan areas, catering to patients not in the city as defined by the country’s healthcare system.
2. **Statistical methods**
3. This is a cross-sectional point prevalence observational study.
4. Categorical variables will be expressed as frequencies and percentages. Continuous variables will be expressed as means, standard deviations and confidence intervals, and medians and interquartile range, as appropriate. For comparisons, Student’s *t* test, the Mann-Whitney U test and the chi-square test will be used. All tests will be two-tailed, and a p value of < 0.05 will be considered statistically significant.
5. Prevalence of sepsis as a proportion of the total number of patients within the ICU on the days of the data collection will be recorded. Causes, outcomes, and time to the management of sepsis will be recorded. Comparisons will be made between low-income, middle-income, and high-income countries and regions.
6. To identify the independent predictors of hospital mortality for sepsis, multivariable logistic regression analysis using models that include the achievement of individual bundle targets and all the variables collected for patients’ characteristics, organisational characteristics, and the World Bank income classification. The first regression model will assess targets required for all patients (lactate measurement, blood cultures, antibiotics). Another regression model, which includes fluid bolus as a target, will be used for the subset of patients with hypotension and/or hyperlactatemia. Covariates are classified into target met, target not met, and target not required, as appropriate. Multicollinearity will be looked for, and model fit assessed with the Hosmer-Lemeshow goodness of fit test.
7. Receiver operating characteristic (ROC) curves will be constructed and the corresponding area under the ROC curves calculated (AUROC) to ascertain the performance of SOFA, qSOFA, and SIRS to predict mortality for all patients with sepsis. The diagnostic performance (sensitivity, specificity, positive and negative predictive values) of SOFA > 2, qSOFA > 2, and SIRS > 2 will be determined.
8. *Appendix 3* details the proposed tables in the eventual paper.
9. **Study management**

**Steering committee**

This will comprise at least 1 national coordinator per country. The national coordinators will invite ICUs in their respective countries and regions to participate in the study. A mix of methods and sampling frames will be used to maximise participation and ensure that the ICUs included are as representative of each country and region as possible. Where available, lists of ICUs, ICU directors, and ICU physicians obtained from national critical care societies and networks will be used. Where these lists are incomplete or unavailable, regional and personal snowball sampling will be used as a supplementary or sole method.

**ICU representative**

Each ICU will have an ICU representative. This can be the ICU director or otherwise. The representative or his/her delegate(s) will:

1. Coordinate any required ethical review by the institutional review board according to local practice.
2. Coordinate the screening and enrolling of patients for the study.
3. Coordinate the data collection and entry into the standardised case report forms online.
4. Liaise with the steering committee for any queries. The steering committee will check the online case report forms for completeness and uniformity and liaise with the ICU representative to clarify any potential errors or missing data.

**Data management**

1. Data are keyed in using pre-designed online standardised case report forms.
2. Only the steering committee, site investigator and research coordinators will have username and password access to enter data into these online forms.
3. The online forms will not capture any patient identifiers such as names or identity card or social security numbers. They will only capture patient index numbers, which are specially created for this study. Only the ICU representative will have a list, which identifies these patients using their patient index numbers. This list is kept at the individual sites and not shared online.
4. All data captured via the online case report forms will be stored in password protected computers.
5. These data will be stored for 10 years, after which they were be deleted.

**Queries**

Queries may be addressed to Dr Andrew Li (andrew\_yunkai\_li@nuhs.edu.sg).

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**Appendix 1**

**ONLINE CASE REPORT FORM**

1. Patient index number \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
2. Admission date to hospital (DDMMYY) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
3. Admission date to ICU (DDMMYY) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
4. Age \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
5. Gender \_(drop down list)\_
6. Comorbidities (tick appropriate boxes)

|  |  |
| --- | --- |
| Cardiovascular disease | Yes/No |
| Chronic lung disease | Yes/No |
| Chronic neurological disease | Yes/No |
| Chronic kidney disease  | Yes/No |
| Peptic ulcer disease | Yes/No |
| Chronic liver disease | Yes/No |
| DM | Yes/No |
| HIV | Yes/No |
| Connective tissue disease | Yes/No |
| Immunosuppression | Yes/No |
| Haematological conditions | Yes/No |
| Malignancy | Yes/No |

1. Type of admission \_(drop down list)\_
2. Source of admission \_(drop down list)\_
3. Vital signs (upon admission to ICU)

Mean blood or arterial pressure (mmHg) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Systolic blood pressure (mmHg) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Heart rate (beats per min) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Temperature (degree Celsius) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Respiratory rate (breaths per min) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Glasgow Coma Scale \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Blood investigations

Total white cell count (x109/L) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Platelets (x109/L) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Haemoglobin (g/dl) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Haematocrit (%) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Sodium (mmol/l) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Potassium (mmol/l) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Creatinine (mmol/l) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Bilirubin (mmol/l) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

pH \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

PaO2 (mmHg)\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

FiO2 (mmHg) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

PaO2/FiO2 ratio \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Severity of illness scores

qSOFA at time of ICU admission \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

SOFA at time of ICU admission \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

SIRS at time of ICU admission \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

APACHE II (over first 24 hours of ICU admission) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Site of infection (multiple choices)
2. Positive cultures (multiple choices)
3. Positive serologies, molecular, or histological tests (multiple choices)
4. Clinical diagnosis made and persisted with due to strong clinical suspicion even though cultures, serologies, molecular, and/or histological tests were performed and negative \_(drop down list)\_
5. Clinical diagnosis made and persisted with due to strong clinical suspicion because cultures, serologies, molecular, and/or histological tests are not available in the ICU \_(drop down list)\_
6. Time zero (DDMMYY HHMM) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
7. Blood culture

Was blood culture performed between 1 hour before time zero to anytime after time zero \_(drop down list)\_

If yes, time of blood culture (DDMMYY HHMM)

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Lactate measurement

Was lactate measured between 1 hour before time zero to anytime after time zero

\_(drop down list)\_

If yes, time of lactate measurement (DDMMYY HHMM) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Antibiotic administration

Was antibiotic administered between 1 hour before time zero to anytime after time zero

 \_ (drop down list)\_

If yes, time of antibiotic administration (DDMMYY HHMM) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Fluid bolus

Was there any episode of hypotension (SBP < 90 mmHg or mean blood pressure or MAP < 65 mmHg) between time zero and 3 hours after time zero?

\_(drop down list)\_

Was any lactate measurement > 2 mmol/L between time zero and 3 hours after time zero?

\_(drop down list)\_

If yes to any of the above, amount of fluid bolus administered within 3 hours of time zero (mLs)

 \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Resources used in ICU (anytime in the current ICU stay; tick the appropriate boxes)

Vasopressors/inotropes \_(drop down list)\_

Mechanical ventilation (MV), performed through a laryngeal mask, an endotracheal, endobronchial or tracheostomy tube \_(drop down list)\_

Duration of MV, defined as from the time of starting invasive MV until the patient has been successfully extubated or breathing on a tracheostomy mask for ≥ 48 hours, whichever comes first (days)

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Noninvasive ventilation (NIV) using NIPPV or CPAP

(excludes NIV used peri-intubation and extubation)

\_(drop down list)\_

Duration of NIV, defined as from the time of starting NIV until the patient has been successfully weaned off for > 24 hours or required subsequent intubation, whichever comes first (days)

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

High-flow nasal cannula (HFNC) \_(drop down list)\_

(excludes HFNC used peri-intubation and extubation)

Duration of HFNC, defined as from the time of starting HFNC until patient has been successfully weaned off for > 24 hours or required subsequent intubation, whichever comes first (days)

 \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Renal replacement therapy (IHD, PD, SLED or CRRT) \_(drop down list)\_

Transfusion of packed red blood cells

 \_(drop down list)\_

Transfusion of platelets \_(drop down list)\_

Transfusion of fresh frozen plasma \_(drop down list)\_

Non-surgical source control measure implemented

e.g. removal of infected intravascular or other catheters,

insertion of ascitic drains, pleural drains, percutaneous drains,

and others \_(drop down list)\_

Surgical source control measure implemented

e.g. debridement of infected necrotic tissue

 \_(drop down list)\_

Time of first source control measure, if any (DDMMYY HHMM)

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Limitation of life-sustaining treatments

Do-not-resuscitate (DNR) order \_(drop down list)\_

Withdrawal of life-sustaining treatments \_(drop down list)\_

Withholding of life-sustaining treatments \_(drop down list)\_

1. Outcome (only 1 choice allowed) \_(drop down list)\_

1. Discharge date from current ICU stay or death date in current ICU stay (DDMMYY) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
2. Discharge date from current hospital stay or death date in current hospital stay (DDMMYY) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**APPENDIX 2**

**ICU Questionnaire**

1. Name of person entering data: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

2. Country: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(drop down list)

3. Hospital: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(drop down list)

4. ICU: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(drop down list)

5. Type of hospital:

Rural

Urban

6. University or university-affiliated hospital \_\_\_\_\_\_(Drop down list)

7. Number of beds in hospital: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(numerical)

8. Type of ICU: Tick one: (only 1 choice allowed)

Medical

Surgical

Mixed medical and surgical

Others (excluding paediatric, coronary and neurosurgical ICUs)

9. Number of beds in ICU: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(numerical)

10. Nurse to ICU patient ratio (tick one): (only 1 choice allowed, choose the ratio most frequently seen in your ICU)

* 1 or more nurses : 1 patient
* 1 nurse : 2 patients
* 1 nurse : 3 patients
* 1 nurse : 4 or more patients

11. Nature of ICU (tick one): (only 1 choice allowed)

* Closed ICU = All patients are cared for by 1 team of intensivists in collaboration with a primary service. Only intensivists have admitting privileges to the ICU.
* Open ICU = Any physician can admit patients to the ICU. The primary service (not intensivists) takes main responsibility for care of patients. If an ICU functions as an open ICU some of the time, and as a closed ICU some of the time, please tick “Open ICU”. Skip question 12 and go to question 13.
1. Only for closed ICUs: Intensivist to ICU patient ratio (tick one): (only 1 choice allowed, choose the ratio most frequently seen in your ICU)
* 1 intensivist : 5 or fewer patients
* 1 intensivist : 6 to 8 patients
* 1 intensivist : 9 to 11 patients
* 1 intensivist : 12 to 14 patients
* 1 intensivist : 15 or more patients
1. Is the ICU part of an accredited intensive care fellowship programme?
* Yes
* No

14. Capabilities

* Able to perform routine blood, urine, stool, CSF, synovial, fluid cultures
* Able to process AFB smear and cultures
* Able to perform PCR testing for tuberculosis
* Able to perform serology or PCR testing for dengue
* Able to perform serology or PCR testing for influenza
* Able to test for galactomannan
* Able to perform blood film identification for malaria

15. Possible additional practices in the general ward outside of the ICU and outside of any high dependency or intermediate care ward or dialysis unit

* Able to support patients on noninvasive ventilation in the general ward
* Able to support patients on invasive mechanical ventilation in the general ward
* Able to support patients on vasopressor/inotrope infusions in the general ward
* Able to support patients on dialysis/renal replacement therapy in the general ward

**APPENDIX 3**

**DATA PRESENTATION**

Table 1: Baseline characteristics

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristics | Overall results | Low-income countries | Middle-income countries | High-income countries | p value |
| Demographics |
| Age, median (IQR), years |  |  |  |  |  |
| Gender, male (%) |  |  |  |  |  |
| Comorbidities |
| Cardiovascular disease |  |  |  |  |  |
| Chronic lung disease |  |  |  |  |  |
| Chronic neurological disease |  |  |  |  |  |
| Chronic kidney disease |  |  |  |  |  |
| Chronic liver disease |  |  |  |  |  |
| DM |  |  |  |  |  |
| HIV |  |  |  |  |  |
| Immunosuppression |  |  |  |  |  |
| Haematological conditions |  |  |  |  |  |
| Solid malignant tumours |  |  |  |  |  |
| Type of admission |
| Medical |  |  |  |  |  |
| Elective surgical |  |  |  |  |  |
| Unscheduled surgical |  |  |  |  |  |
| Source of admission |
| Emergency department (ED) |  |  |  |  |  |
| Operating room |  |  |  |  |  |
| General wards |  |  |  |  |  |
| Inter-hospital transfer |  |  |  |  |  |
| Site of infection |
| Respiratory |  |  |  |  |  |
| Urinary tract |  |  |  |  |  |
| Abdomen |  |  |  |  |  |
| Neurological |  |  |  |  |  |
| Bones and joints |  |  |  |  |  |
| Soft tissue and skin |  |  |  |  |  |
| Intravascular catheter |  |  |  |  |  |
| Infective endocarditis |  |  |  |  |  |
| Primary bacteraemia |  |  |  |  |  |
| Systemic |  |  |  |  |  |
| Unknown |  |  |  |  |  |
| Others |  |  |  |  |  |
| Organ dysfunction, N (%), as per SOFA definition |
| Respiratory |  |  |  |  |  |
| Cardiovascular |  |  |  |  |  |
| Renal |  |  |  |  |  |
| Neurologic |  |  |  |  |  |
| Coagulation |  |  |  |  |  |
| Hepatic |  |  |  |  |  |
| Severity, median (IQR) |
| APACHE II |  |  |  |  |  |
| SIRS |  |  |  |  |  |
| SOFA |  |  |  |  |  |
| qSOFA |  |  |  |  |  |

Table 2: Pathogens

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristics | Overall results | Low-income countries | Middle-income countries | High-income countries | p value |
| Gram positive bacteria |
| Methicillin-sensitive *Staphylococcus aureus* |  |  |  |  |  |
| Methicillin-resistant *Staphylococcus aureus* |  |  |  |  |  |
| *Streptococcus pneumonia* |  |  |  |  |  |
| Other *Streptococcus* species |  |  |  |  |  |
| *Enterococcus* |  |  |  |  |  |
| *Clostridium tetani* |  |  |  |  |  |
| Others |  |  |  |  |  |
| Gram negative bacteria |
| *Klebsiella pneumonia* |  |  |  |  |  |
| *Escherichia coli* |  |  |  |  |  |
| *Pseudomonas aeruginosa* |  |  |  |  |  |
| *Acinetobacter baumannii* |  |  |  |  |  |
| *Bulkholderia pseudomallei* |  |  |  |  |  |
| *Enterobacter cloacae* |  |  |  |  |  |
| *Haemophilus influenza* |  |  |  |  |  |
| *Salmonella* species |  |  |  |  |  |
| *Citrobacter* species |  |  |  |  |  |
| *Stenotrophomonas maltophilia* |  |  |  |  |  |
| *Proteus* species |  |  |  |  |  |
| *Bacteroides fragilis* |  |  |  |  |  |
| *Leptospira* species |  |  |  |  |  |
| *Coxiella burnetti* |  |  |  |  |  |
| *Rickettsia* species |  |  |  |  |  |
| Gram indeterminate bacteria |
| *Mycobacterium tuberculosis* |  |  |  |  |  |
| Non-tuberculous mycobacteria |  |  |  |  |  |
| Fungi |
| *Candida albicans* |  |  |  |  |  |
| *Candida* non-*albicans* |  |  |  |  |  |
| Aspergillus |  |  |  |  |  |
| Blastomycocis |  |  |  |  |  |
| Histoplasmosis |  |  |  |  |  |
| Cryptococcus |  |  |  |  |  |
| Parasites |
| Malaria |  |  |  |  |  |
| Viruses |
| Rabies |  |  |  |  |  |
| Measles |  |  |  |  |  |
| Chikungunya |  |  |  |  |  |
| Dengue |  |  |  |  |  |
| Influenza  |  |  |  |  |  |

Data presented will include all positive cultures, histological, serological, and molecular tests, as well as clinical diagnoses (either due to strong clinical suspicion despite negative tests or non-availability of specific tests). Footnotes will enumerate number of patients for which clinical diagnoses alone were made.

Table 3: Time to management according to Surviving Sepsis Campaign’s 3-hour bundle in sepsis

|  |  |  |  |
| --- | --- | --- | --- |
|  | Survivors | Non-survivors | pvalue |
| Low-income countries | Middle-income countries | High-income countries | Low-income countries | Middle-income countries | High-income countries |
| Compliance |
| Full bundle within 3 hours |  |  |  |  |  |  |  |
| Blood cultures within 1 hour |  |  |  |  |  |  |  |
| Antibiotics within 1 hour |  |  |  |  |  |  |  |
| Lactate measurement within 3 hours |  |  |  |  |  |  |  |
| Fluid resuscitation (30mL/kg) within 3 hours |  |  |  |  |  |  |  |
| Time to management, median minutes (IQR) |
| Blood cultures |  |  |  |  |  |  |  |
| Antibiotics |  |  |  |  |  |  |  |
| Lactate measurement |  |  |  |  |  |  |  |
| Fluid resuscitation |  |  |  |  |  |  |  |

Table 4: Outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristics | Overall results | Low-income countries | Middle-income countries | High-income countries | p value |
| Mortality, N (%) |
| Hospital |  |  |  |  |  |
| ICU |  |  |  |  |  |
| Length of stay, median days (IQR) |
| Hospital |  |  |  |  |  |
| ICU |  |  |  |  |  |

Table 5: Variables independently associated with hospital mortality

|  |  |  |
| --- | --- | --- |
| Variable | Adjusted odds ratio (95% CI) | p value |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

Table 6: Diagnostic performance for the prediction of hospital mortality

|  |  |  |  |
| --- | --- | --- | --- |
| Prediction of death | SIRS | SOFA | qSOFA |
| Sensitivity, % (95% CI) |  |  |  |
| Specificity, % (95% CI) |  |  |  |
| Predictive value, % (95% CI) |
| Negative |  |  |  |
| Positive |  |  |  |
| Likelihood ratio (95% CI)  |
| Negative |  |  |  |
| Positive |  |  |  |
| AUROC, (95% CI) |  |  |  |

Supplementary table 1: Distribution of participating ICUs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Participating sites | Number of hospitals | Number of ICUs | Number of patients with sepsis | Number of patients with infection | Total number of ICU patients | Total number of patients in hospital |
| Low-income countries |  |  |  |  |  |  |
| Middle-income countries |  |  |  |  |  |  |
| High-income countries |  |  |  |  |  |  |

Supplementary table 2: ICU characteristics

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristics | All | Low-income countries | Middle-income countries | High-income countries | p value |
| All ICUs |  |  |  |  |  |
| Type of ICU, N (%) |
| Open  |  |  |  |  |  |
| Closed |  |  |  |  |  |
| Urban |  |  |  |  |  |
| Rural |  |  |  |  |  |
| University |  |  |  |  |  |
| ICU specialty, N (%) |
| Medical |  |  |  |  |  |
| Surgical |  |  |  |  |  |
| Mixed |  |  |  |  |  |
| ICU resources |
| ICU beds, N (%) |
| 1-6 |  |  |  |  |  |
| 7-10 |  |  |  |  |  |
| 11-20 |  |  |  |  |  |
| >20 |  |  |  |  |  |
| Nurse to patient ratio, N (%) |
| >1:1 |  |  |  |  |  |
| 1:2 |  |  |  |  |  |
| 1:3 |  |  |  |  |  |
| 1:>4 |  |  |  |  |  |
| Intensivist to patient ratio, N (%) |
| 1:<5 |  |  |  |  |  |
| 1:6-10 |  |  |  |  |  |
| 1:>11 |  |  |  |  |  |
| Training programme in ICU, N (%) |
| Yes |  |  |  |  |  |
| No |  |  |  |  |  |

Supplementary table 3: Treatments

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Treatment | All | Low-income countries | Middle-income countries | High-income countries | p value |
| Vasopressors/inotropes |  |  |  |  |  |
| Mechanical ventilation |  |  |  |  |  |
|  Duration, median (IQR) |  |  |  |  |  |
| NIV |  |  |  |  |  |
|  Duration, median (IQR) |  |  |  |  |  |
| High flow nasal cannula |  |  |  |  |  |
|  Duration, median (IQR) |  |  |  |  |  |
| Vasopressors/inotropes |  |  |  |  |  |
| Renal replacement therapy |  |  |  |  |  |
| Red blood cell transfusion |  |  |  |  |  |
| Platelet transfusion |  |  |  |  |  |
| Fresh frozen plasma transfusion |  |  |  |  |  |
| Surgical source control |  |  |  |  |  |
| Non-surgical source control |  |  |  |  |  |