Retrospective observational cohort study of patients diagnosed with sepsis: Is this really sepsis?

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Abstract

Background

Sepsis-3 defines sepsis as a life-threatening organ dysfunction due to a dysregulated host response to infection. Measuring a dysregulated host response is difficult in practice, so patients with organ dysfunction due to other causes, such as an underlying comorbidity or the direct effects of infection, may be diagnosed with sepsis. We aimed to characterise patients diagnosed with sepsis and meeting the sepsis-3 criteria according to whether organ dysfunction was potentially due to a dysregulated immune response or an alternative cause.

Methods

We undertook a single-centre, retrospective, observational study of patients admitted to hospital with sepsis between 1/1/2022 and 31/12/2022. We reviewed clinical, laboratory, and imaging records to determine whether cases met sepsis-3 criteria and whether organ dysfunction was more likely to be due to a dysregulated immune response or an identifiable alternative explanation.

Results

We analysed 373 cases, of whom 303 (81.2%) fulfilled the sepsis-3 criteria. Of these, 78 (25.7%, 95% confidence interval 21.4%-30.0%) had an alternative explanation for their organ dysfunction, with 28 (9.2%) due to exacerbation of a comorbidity, 42 (13.9%) due to the direct effects of infection, and 8 (2.6%) involving evidence of respiratory dysfunction based on 'normal' oxygen saturation measurements. Patients with an alternative explanation for their organ dysfunction tended to be less acutely ill (median [interquartile range] National Early Warning Score 5 [3-8] versus 7 [5-10], $p<0.001$) and have lower in-hospital mortality than (19.2% versus 34.7%, $p=0.011$) than those who were more likely to have a dysregulated host response.

Conclusion

Around a quarter of patients diagnosed with sepsis and meeting the sepsis-3 criteria were unlikely to have a dysregulated immune response causing their organ dysfunction. Focusing sepsis diagnosis on those most likely to have a dysregulated immune response could identify patients who are most likely to benefit from sepsis treatment and could improve sepsis care.

What is already known on this topic:

The sepsis-3 definition of sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection. We are currently unable to directly measure the dysregulated host response in clinical practice. Patients with alternative explanations for their organ dysfunction, such as the direct effects of infection on an organ or exacerbation of a comorbidity due to the nonspecific effects of infection, may meet the sepsis-3 definition without having a dysregulated host response.

What this study adds:

This retrospective observational cohort study showed that 78/303 patients (25.7%) who were diagnosed with sepsis and met the sepsis-3 definition had alternative explanations for their organ dysfunction that were more likely than a dysregulated host response. These patients tended to be less acutely ill and have lower in-hospital mortality.

How this study might affect research, practice or policy:

Focussing upon the patients who are most likely to have a dysregulated immune response in sepsis audit, research, and clinical practice could identify patients who are more likely to benefit from sepsis treatment.

Introduction

Sepsis is a common reason for hospital admission in which the body's reaction to infection leads to major organ failure and life-threatening illness [1]. International consensus definitions of sepsis have changed over the past 35 years [2-4] and the incidence of sepsis has varied markedly [5], potentially due to variation in coding and classification [6]. This has led to conflict between campaigns to increase awareness and identification of sepsis [7] and concerns about 'sepsis hysteria'. [8] Furthermore, the challenge of applying sepsis definitions to older populations with multiple comorbidities [9,10] has led to concerns that sepsis may be a 'failed paradigm' [11]. We need to improve our understanding of how definitions of sepsis apply to patients in practice.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) define sepsis as a life-threatening organ dysfunction due to a dysregulated host response to infection. [4] The pathobiology of sepsis is uncertain, but the dysregulated host response is recognised to involve both pro- and anti-inflammatory responses, along with major changes in nonimmunologic pathways, that lead to organ dysfunction. [4] No current clinical measures reliably reflect the concept of a dysregulated host response, [4] so the sepsis-3 definition is based upon evidence of infection alongside organ dysfunction, determined using the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score. [12] The SOFA score (Table 1) uses clinical and laboratory markers to allocate up to four points for dysfunction in each major organ system (respiration, coagulation, liver, cardiovascular, central nervous system (CNS), and renal). The sepsis-3 definition uses an acute change in total SOFA score of two or more points consequent to the infection to identify organ dysfunction.

Table 1: The Sequential (sepsis-related) Organ Failure Assessment (SOFA) score

Organ Dysfunction	Score				
	0	**1**	**2**	**3**	**4**
PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200	<100*
Platelet Count ($x10^9/L$)	≥150	<150	<100	<50	<20
Bilirubin (µmol/L)	<20	20-32	33-101	102-204	>204

Hypotension	MAP ≥70	MAP <70	Dopamine ≤5 Or Dobutamine (any dose)	Dopamine >5 Or Epinephrine ≤0.1 Or Norepinephrine ≤0.1	Dopamine >15 Or Epinephrine >0.1 Or Norepinephrine >0.1
Glasgow Coma Score	15	13-14	10-12	6-9	<6
Creatinine (µmol/L)	<110	110-170	171-299	300-440 Or Urine Output <500ml/day	>440 Or Urine Output <200ml/day

PaO2: Partial pressure of arterial oxygen; FiO2: Fraction of inspired oxygen; MAP: Mean arterial pressure (mmHg)

Organ dysfunction, as determined by the SOFA score, may be consequent upon infection without being due to a dysregulated host response [10]. Direct effects upon the infected organ, such as respiratory failure in respiratory infection, may result in organ dysfunction. Nonspecific effects of infection, such as fluid imbalance or fever, occurring in the presence of underlying comorbidities, such as chronic kidney disease or dementia, can lead to acute changes in the SOFA score. Direct effects and exacerbation of comorbidity may occur in combination, such as in an infective exacerbation of chronic lung disease. In all these cases, patients may meet the sepsis-3 definition without a dysregulated host response to infection being likely. Such patients may have markedly different characteristics, outcomes, and treatment requirements to those with 'genuine' sepsis (i.e. with organ dysfunction more likely to be due to a dysregulated host response).

Table 2 shows three hypothetical examples of cases that meet the sepsis-3 definition but have clear explanations for their acute change in SOFA score unrelated to a dysregulated immune response. In each case we assume that the patient's baseline (pre-admission) SOFA score was zero. Case 1 has hypoxia due to the direct effects of pneumonia on the lungs. Case 2 has a reduced Glasgow Coma Scale (GCS) due to hypoactive delirium triggered by a urinary tract infection. Case 3 has elevated creatinine due to viral gastroenteritis causing fluid loss on a background of chronic kidney disease. In each case the sepsis-3 definition is only met because of a change in SOFA score that has a clear explanation. We cannot exclude the possibility of a dysregulated immune response, but the presence

of a clear alternative explanation means that we have no need to postulate a dysregulated immune response (that we cannot measure) as the cause for their organ dysfunction.

Table 2: Case examples that meet the sepsis-3 criteria but are unlikely to have organ dysfunction due to a dysregulated immune response

Case	Case description	SOFA score
1	A previously healthy 56-year-old man presents with fever, dyspnoea and productive cough. Vital signs show heart rate 115/min, blood pressure 135/82, respiratory rate 25/min, peripheral oxygen saturation 94% on 60% FiO2, GCS 15, and temperature 39.1 °C. Blood tests show raised white cell count and C-reactive protein, PaO2 79mmHg on 60% FiO2, platelet count 243 $x10^9$/L, creatinine 95 µmol/L and bilirubin 18 µmol/L. Chest x-ray shows right sided consolidation.	2
2	An 86-year-old female with dementia presents with low grade fever, urinary incontinence, and reduced consciousness. Vital signs show heart rate 72/min, blood pressure 146/94, respiratory rate 14/min, peripheral oxygen saturation 97% on air, GCS 12, and temperature 37.8 °C. Blood tests show raised white cell count and C-reactive protein, platelet count 382 $x10^9$/L, creatinine 73 µmol/L and bilirubin 13 µmol/L. Urine culture grows E Coli.	2
3	A 78-year-old man with hypertension and chronic kidney disease (stage 2) presents with diarrhoea, vomiting, poor oral intake and mild confusion. Vital signs show heart rate 93/min, blood pressure 142/74, respiratory rate 16/min, peripheral oxygen saturation 96% on air, GCS 15, and temperature 38.2 °C. Blood tests show raised C-reactive protein, platelet count 276 $x10^9$/L, creatinine 193 µmol/L (previously 105) and bilirubin 17 µmol/L. Stool sample is positive for norovirus.	2

We aimed to determine the proportion of patients diagnosed with sepsis and meeting the sepsis-3 criteria who had a clear cause for their organ dysfunction, such as exacerbation of a comorbidity and or direct effects of infection, and then compare the characteristics of these patients to those whose organ dysfunction was more likely due to a dysregulated immune response.

Methods

We undertook a single-centre retrospective observational cohort study at the Northern General Hospital in Sheffield, England. The Northern General Hospital emergency department (ED) is the only adult ED serving the approximate half million population of Sheffield. Children (aged 16 or less) and obstetric cases are managed at other hospitals in Sheffield.

The Scientific Computing Department identified all adults admitted through the ED who received a 3-digit International Classification of Diseases version 10 (ICD-10) code of A40 (streptococcal sepsis) or A41 (other sepsis) between 1/1/2022 and 31/12/2022, having excluded repeat admissions by the same patient. We sorted cases according to their alphanumeric hospital number and then consecutively reviewed the hospital records of eligible cases and excluded cases where there was no mention of sepsis in the initial five days of admission, where the ICD10 coding appeared to be an error, or where there was insufficient information recorded to assess the case.

We collected anonymised data from the hospital records of eligible cases using an Excel spreadsheet. Data included patient characteristics (age, sex, comorbidities in the Charleson Comorbidity Index, [13] and Clinical Frailty Score [14]), presenting physiology, blood markers of infection, microbiological and radiological evidence of infection, variables required to calculate the SOFA score up to five days after admission, whether the patient was admitted to critical care, length of hospital stay, and date of death.

Evidence of infection was categorised into clinical, radiological, laboratory and microbiological evidence, according to a modified version of the Linder-Mellhammar Criteria of Infection (LMCI). [15] This involves scoring the evidence of infection from zero to four in each anatomical category based on specified criteria. Scores of zero to one indicate no infection, while scores of two, three and four respectively indicate possible, probable, and definite infection. We categorised scores of three or four as providing evidence of infection. We modified the LMCI infection categories by separating intra-abdominal infections into hepatobiliary and non-hepatobiliary, adding infective endocarditis (based on the modified Duke's criteria) and providing an 'unclear' category when the focus of infection could not be identified.

We used clinical and laboratory measurements up to five days after admission to calculate the worst SOFA score in the first five days. In cases with no arterial blood gas recording, we estimated the ratio of the partial pressure of arterial oxygen from the peripheral oxygen saturation [16]. In accordance

with the sepsis-3 definition, [4] we assumed the baseline (pre-admission) SOFA score would be zero unless there was evidence in the hospitals records to suggest otherwise. The National Early Warning Score version 2 (NEWS2) was calculated from the first observations recorded after ED arrival.

The sepsis-3 definition was met if the patient had evidence of infection and a change from baseline to worst SOFA score of two points or more. Cases meeting the sepsis-3 definition were then reviewed to identify causes of organ dysfunction other than a dysregulated host response.

We identified patients with respiratory, hepatobiliary, or CNS infection who had corresponding acute changes in the respective respiratory, liver and CNS elements of the SOFA score. We recalculated the worst SOFA score with the points for the relevant element removed and determined whether the sepsis-3 criteria were still met. If not, we assumed that the direct effects of infection were likely to have explained the organ dysfunction identified by the SOFA score rather than a dysregulated host response. For example, for case 1 in table 2 we would have removed the 2 points on the SOFA score relating to respiratory dysfunction, leaving an adjusted SOFA score of zero.

We then identified patients with chronic kidney disease or dementia who had corresponding acute changes in the respective renal and CNS elements of the SOFA score. If recalculation of the worst SOFA score with these points removed resulted in the sepsis-3 criteria not being met, we assumed that exacerbation of chronic kidney disease or delirium on a background of dementia was likely to have explained the organ dysfunction rather than a dysregulated immune response. For example, for case 2 in table 2 we would have removed the 2 points on the SOFA score relating to reduced conscious level and for case 3 we would have removed the 2 points relating to renal dysfunction, leaving an adjusted SOFA score of zero for each case.

Finally, we noted that using peripheral oxygen saturation to assess respiratory function resulted in patients with oxygen saturation of 94-95% on air being allocated a point on the SOFA score. These values are within the target oxygen saturation range of 94-98% recommended in guidelines from the National Institute for Care Excellence (NICE) [1] and the UK Sepsis Trust [7]. We therefore identified cases that only met the sepsis-3 criteria if the worst SOFA score included a point for oxygen saturation of 94-95% on air.

We undertook analysis using Statistical Package for Social Sciences (SPSS) Version 29.0.1.0 to report key proportions with 95% CI for patient groups according to whether a dysregulated host response or

an alternative cause was more likely to explain their organ dysfunction. We compared the characteristics of patients in whom a dysregulated host response was more likely to those in whom an alternative cause was more likely using a Chi-square test or Fisher's Exact test for categorical variables or a Mann-Whitney test for continuous variables, with $p<0.05$ considered to be statistically significant. The planned overall sample size was 500 cases. We assumed that 50% (N=250 would meet the sepsis-3 definition, based on a similar previous study [9], which would allow estimation of a 20% proportion in those meeting the sepsis-3 definition with a 95% confidence interval (CI) from 15.2% to 25.5%.

Patient and public involvement

We met with the Sheffield Emergency Care Forum (SECF), an advisory group consisting of patients and members of the public [17], to explain the project rationale, methods, and public importance, and seek their feedback and advice.

Ethical approval

The UK Health Research Authority approved the study as a low-risk project that did not require full National Health Service ethics committee review (reference 23/HRA/1873). The University of Sheffield Research Ethics Committee approved the project as a low-risk educational project (reference 056861).

Results

We identified 626 first attendances with an ICD10 code for sepsis and selected 400 for review. We excluded 27/400 with no mention of sepsis in the first five days (N=21), apparent coding error (N=4), or insufficient information (N=2), leaving 373 cases for analysis. The median age was 80 years (interquartile range [IQR] 71.5 to 85) and 205 (55.0%) were male. The mean Charleson Comorbidity Index was 5.3 (standard deviation [SD] ±2.13) and the mean Clinical Frailty Score was 5.91 (SD ±1.32). The most common comorbidities were chronic kidney disease (33.2%), diabetes (30.0%), dementia (25.5%), respiratory disease (24.4%) and congestive heart failure (18.2%).

Figure 1 shows the flow chart of cases through the study, including classification according to the sepsis-3 definition and the likely cause of organ dysfunction. The sepsis-3 definition was met in 303/373 (81.2%, 95% CI 74.9% to 87.6%), while 16 cases had insufficient evidence of infection (LMCI score <3), 29 cases had a worst SOFA score of <2, and 25 cases had an acute change in SOFA score from baseline of <2.

We identified 42 patients (13.9%, 95% CI 7.3% to 20.4%) with a change in SOFA score explained by the direct effects of either a respiratory infection (N=29), hepatobiliary infection (N=10) or both (N=3). We then identified 28 patients (9.2%, 95% CI 6.8% to 11.6%) with a change in SOFA score explained by a raised creatinine in a patient with chronic kidney disease (N=15) or altered consciousness in a patient with known dementia (N=13). Finally, we identified eight patients (2.6%, 95% CI 0.3% to 4.9%) who only met the sepsis-3 criteria when the change in SOFA score included a point for having a peripheral oxygen saturation of 94-95% on room air. Overall, 78 patients (25.7%, 95% CI 21.4% to 30.0%) meeting the sepsis-3 criteria had a cause for their organ dysfunction that appeared to be more likely than a dysregulated host response to infection.

Table 3 shows the baseline characteristics of the patients. There were no marked differences between patients with organ dysfunction more likely due to a dysregulated host response and those with organ dysfunction due to an alternative cause.

Table 3: Baseline characteristics comparing patients with organ dysfunction more likely due to a dysregulated host response to those with organ dysfunction more likely due to an alternative cause

	All sepsis-3 cases (n = 303)	Dysregulated host response more likely (n = 225)	Alternative cause more likely (N=78)	P-value
Age (Years), Median (IQR)	80 (73-86)	79 (71-85)	82 (76-87)	0.029
Sex, n (%)				
Male	168 (55.4%)	129 (57.3%)	39 (50.0%)	0.261
Female	135 (44.6%)	96 (42.7%)	39 (50.0%)	
Charleson Comorbidity Index, Mean (±SD)	5.30 (±2.08)	5.29 (±2.16)	5.33 (±1.86)	0.816
Co-Morbidities, n (%)				
Myocardial Infarction	20 (6.6%)	16 (7.1%)	4 (5.1%)	0.791
Congestive Heart Failure	54 (17.8%)	44 (19.6%)	10 (12.8%)	0.180
Peripheral Vascular	14 (4.6%)	12 (5.3%)	2 (2.6%)	0.531
Disease	43 (14.2%)	34 (15.1%)	9 (11.5%)	0.572
Cerebrovascular Accident	81 (26.7%)	54 (24.0%)	27 (34.6%)	0.068

Dementia	71 (23.4%)	54 (24.0%)	17 (21.8%)	0.692
Respiratory Disease	10 (3.3%)	8 (3.6%)	2 (2.6%)	1.000
Connective Tissue Disease	2 (0.7%)	2 (0.9%)	0 (0.0%)	1.000
Peptic Ulcer Disease	5 (1.7%)	4 (1.8%)	1 (1.3%)	1.000
Liver Disease	89 (29.4%)	64 (28.4%)	25 (32.1%)	0.547
Diabetes Mellitus	18 (5.9%)	15 (6.7%)	3 (3.8%)	0.578
Hemiplegia	104 (34.3%)	72 (32.0%)	32 (41.0%)	1.000
Chronic Kidney Disease	29 (9.6%)	21 (9.3%)	8 (10.3%)	0.827
Solid Tumour Cancer – Localised	17 (5.6%)	14 (6.2%)	3 (3.8%)	0.537
Solid Tumour Cancer – Metastatic				
Clinical Frailty Score, Mean (±SD)	5.95 (±1.34)	6.04 (±1.36)	5.72 (±1.25)	0.040
Baseline SOFA Score, n (%)				
0	179 (59.1%)	128 (56.9%)	51 (65.4%)	0.189
1	72 (23.8%)	58 (25.8%)	14 (17.9%)	0.162
2	30 (9.9%)	22 (9.8%)	8 (10.3%)	1.000
3	18 (5.9%)	15 (6.7%)	3 (3.8%)	0.578
4	2 (0.7%)	1 (0.4%)	1 (1.3%)	0.449
5	2 (0.7%)	1 (0.4%)	1 (1.3%)	0.449

IQR: Interquartile range; SD: Standard deviation

Table 4 shows the presenting characteristics and outcomes. Patients who were more likely to have a dysregulated host response had a higher median NEWS2 score (7 versus 5, p<0.001), greater median change from baseline SOFA score (5 versus 2, p<0.001), greater proportion with septic shock (20.5% versus 1.4%, p<0.001) and higher in-hospital mortality (34.7% versus 19.2%, p=0.011).

Table 4: Presenting characteristics and outcomes comparing patients with organ dysfunction more likely due to a dysregulated host response to those with organ dysfunction more likely due to an alternative cause

	All sepsis-3 cases (n = 303)	Dysregulated host response more likely (n = 225)	Alternative cause more likely (N=78)	P-value
Infection Focus, n (%)				
Lower respiratory tract infection	78 (25.7%)	51 (22.7%)	27 (34.6%)	0.038
Urinary tract infection	87 (28.7%)	65 (28.9%)	22 (28.2%)	0.908
Hepatobiliary infection	41 (13.5%)	26 (11.6%)	15 (19.2%)	0.088
Other abdominal infection	8 (2.6%)	6 (2.7%)	2 (2.6%)	1.000
Gastrointestinal infection	4 (1.3%)	4 (1.8%)	0 (0.0%)	0.576
Skin + soft tissue infection	23 (7.6%)	21 (9.3%)	2 (2.6%)	0.079
Bone and joint infection	3 (1.0%)	2 (0.9%)	1 (1.3%)	1.000
CNS infection	2 (0.7%)	2 (0.9%)	0 (0.0%)	1.000
Primary bloodstream infection	5 (1.7%)	5 (2.2%)	0 (0.0%)	0.333
Catheter related infection	23 (7.6%)	18 (8.0%)	5 (6.4%)	0.806
Ear nose or throat infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Neutropenic fever	2 (0.7%)	2 (0.9%)	0 (0.0%)	1.000
Reproductive tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Infective endocarditis	2 (0.7%)	1 (0.4%)	1 (1.3%)	0.449
Unclear	25 (8.3%)	22 (9.8%)	3 (3.8%)	0.150
NEWS2 Score, Median (IQR)	7 (4-9)	7 (5-10)	5 (3-8)	<0.001
NEWS2 Score, n (%)				
0; Very Low Risk	11 (3.6%)	4 (1.8%)	7 (9.0%)	0.008
1-4; Low Risk	81 (26.8%)	51 (22.8%)	30 (38.5%)	0.007
5-6; Moderate Risk	54 (17.9%)	42 (18.8%)	12 (15.4%)	0.504
≥7; High Risk	156 (51.7%)	127 (56.7%)	29 (37.2%)	0.003
Maximum SOFA Score Within 5 Days of Admission, Median (IQR)	5 (3-7)	6 (4-7)	3 (2-4)	<0.001
Acute Change in SOFA Score (Maximum - Baseline),	4 (3-6)	5 (4-7)	2 (2-3)	<0.001

Median (IQR)				
Septic Shock, n (%)	49 (16.2%)	46 (20.5%)	3 (1.4%)	<0.001
Length of Inpatient Stay (Days), Median (IQR)	9 (5-20)	9 (5-19)	11 (5-26)	0.159
Intensive care admission, n (%)	16 (5.3%)	15 (6.7%)	1 (1.3%)	0.080
In-hospital mortality, n (%)	93 (30.7%)	78 (34.7%)	15 (19.2%)	0.011

Discussion

We found that around a quarter of patients who have an ICD10 diagnosis of sepsis and who met the sepsis-3 definition had an explanation for their organ dysfunction that appeared to be more likely that a dysregulated host response. These patients tended to be less acutely ill and have a lower risk of septic shock and death than those who organ dysfunction was more likely to be due to a dysregulated host response. We suggest that these patients are unlikely to have sepsis, defined as life-threatening organ dysfunction consequent upon a dysregulated host response. Including these cases in the practical definition of sepsis contributes to the heterogeneity of the sepsis population and acts as a barrier to developing high quality sepsis care. These cases are relatively easy to define and identify. If others can reproduce our methods and findings, clinical practice and research could be developed to focus on patients who are more likely to have a dysregulated host response and thus benefit from current and future treatments for sepsis.

Previous studies have highlighted the challenges of accurate and reliable diagnostic coding of sepsis. A scoping review of 17 studies [18] identified a variety of ICD coding methods using retrospective chart review and administrative data but determined that none were optimal for identifying sepsis. A systematic review of 13 studies [19] found that ICD10 coding missed most cases identified by chart review or registry databases. Litell et al [20] identified marked discrepancies between sepsis-3 and ICD coding of sepsis in a study of 3121 ED patients with potential sepsis. Atkin et al [21] analysed hospital episodes statistic in England and found that changes in sepsis coding practice altered case-mix and case selection, in ways that varied between centres. These studies have not addressed the specific issue of whether organ dysfunction in sepsis is likely to be due to a dysregulated host response.

Our study has strengths and limitations. We selected patients who had an ICD10 diagnosis for sepsis and determined that they met the sepsis-3 diagnosis to ensure that our cohort consisted of patients

who would be considered to have sepsis in practice. ICD10 coding was done by trained coders using the hospital records and discharge summary, so it could have missed potentially eligible cases. We used the SOFA score, LMIC criteria, and clear criteria for judging direct effects of infection and exacerbation of comorbidities to ensure that our assessments were reproducible, but we did not undertake independent adjudication of these assessments. We restricted our judgements around the direct effects of infection or exacerbations of comorbidities to those that we felt would be widely accepted. More liberal judgements about these factors (and other potential causes of organ dysfunction) could further reduce the proportion of cases where organ dysfunction was considered likely to be due to a dysregulated host response. The alternative causes for organ dysfunction were relatively heterogeneous. Subdividing this group could provide further insights but our study was not powered for such analysis. This was a single-centre study with a relatively small sample size, so our estimates are relatively imprecise and may not be generalisable. We were unable to achieve our planned sample size of 500 due to time constraints, although we exceeded the anticipated sample of 250 meeting the sepsis-3 definition. The 400 cases were selected from the 626 eligible cases in the order of the hospital number, which is not random and may have resulted in a biased sample with biased estimates of the key findings. We aimed to characterise patients grouped according to our classification rather than seek explanations for differences between the groups, so analysis was limited to univariate comparisons. An appropriately designed and powered study would be required to support multivariate analysis to determine what patient characteristics explain the differences in outcome between the groups.

Further research, ideally a large multicentre study, is required to confirm our findings. This could determine whether our approach to determining the likely cause of organ dysfunction in sepsis is reproducible and could be used in audit, research, and clinical practice to identify patients who are most likely to have a dysregulated host response and thus benefit from sepsis care. An appropriately powered study could determine whether the differences in acuity and outcomes we observed are confirmed, further characterise these differences among patients with alternative causes for organ dysfunction and examine for differences in escalation plans or ceilings of treatment.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and have no competing interests to declare.

Contributor and guarantor information

SG conceived and designed the study. HB acquired analysed the data. Both authors interpreted the data. Both authors contributed to drafting the manuscript. SG is the guarantor of the paper. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data Sharing

Anonymised data are available from the corresponding author upon reasonable request (contact details on first page).

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Figure legends

Figure 1: Flow of cases through the study