Persistent critical illness: baseline characteristics, intensive care course, and cause of death

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ABSTRACT

Objectives: Persistent critical illness (PerCI) is associated with high mortality and discharge to institutional care. Little is known about factors involved in its progression, complications and cause of death. We aimed to identify such factors and the time when the original illness was no longer the reason for intensive care unit (ICU) stay.

Design: Retrospective matched case–control study using an accepted PerCI definition (> 10 days in ICU).

Setting: Single-centre tertiary metropolitan ICU.

Participants: All adult patients admitted during a 2-year period were eligible, matched on diagnostic code, gender, age and risk of death.

Main results: Seventy-two patients staying > 10 days (PerCI cases) were matched to 72 control patients. The original illness was no longer a cause for continued ICU stay after a median of 10 days (interquartile range [IQR], 7–16) versus 2 days (IQR, 0–3); $P < 0.001$. Patients with PerCI were more likely to develop new sepsis (52.8% *v* 23.6%; $P < 0.001$), delirium (37.5% *v* 9.7%; $P < 0.001$), ICU-acquired weakness (15.3% *v* 0%, $P = 0.001$), and to be discharged to chronic care or rehabilitation (37.5% *v* 16.7%; $P < 0.005$). Death resulting from sepsis with multi-organ failure occurred in 16.7% *v* 8.3% of control patients ($P = 0.13$), and one-third of patients with PerCI were not mechanically ventilated on Day 10.

Conclusion: PerCI likely results from complications acquired after ICU admission and mostly unrelated to the original illness; by Day 10, the original illness does not appear to be its cause, and new sepsis appears an important association.

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Patients with persistent critical illness (PerCI) are a major therapeutic challenge in modern intensive care units (ICUs) and a source of stress to ICU care teams.[1,2] Although accounting for only a subgroup of all ICU patients, such patients account for 20–55% of all ICU bed-days and have a mortality rate of 25–30%, high rates of discharge to institutional care, and high health care cost burden — exceeding $20 billion annually in the United States alone.[3-5] In Australia and New Zealand, 5% of all critically ill patients develop PerCI, but occupy one-third of the total ICU bed-days.[6] Numerous attempts have been made to characterise this population, using duration of prolonged mechanical ventilation,[4,7] neuroendocrine changes,[8] or alteration of body composition,[9] but no uniform, epidemiologically validated and pragmatically useful definition has previously existed. However, a recent study of over one million patients admitted to 182 ICUs in Australia and New Zealand demonstrated that after 10 days of ICU admission, acute admission diagnosis and physiological derangement were no more predictive of in-hospital mortality than were pre-ICU patient characteristics, thereby defining the onset of PerCI.[6] Similar findings have recently been reported from a study of almost 18 000 critically ill Canadian patients after 9 days in the ICU,[5] thus supporting the robustness of this epidemiological approach to defining PerCI.

Despite these advances in definition, the mechanisms leading to prolonged ICU stay in individual patients remain unclear. In particular, there is nearly no research on the interplay between original reasons for ICU admission, changes in patients' day-to-day ICU course and supports, and ultimate length of stay, outcome and cause of death in non-survivors. Therefore, criteria such as the requirement for prolonged mechanical ventilation that have traditionally been used to categorise this population are likely inadequate to account for the heterogeneity and complexity of this cohort.

Accordingly, we aimed to identify factors both before and during ICU admission discriminating persistently critically ill patients from a matched cohort in a retrospective case–control study. In particular, we hypothesised that factors common to long-stay ICU patients (eg, sepsis and delirium) would more likely be present in patients with PerCI than in controls, and that a transition point could be identified when the original admission diagnosis was no longer the dominant reason for the patient having to remain in the ICU. We further hypothesised that mechanical ventilation would not be the sole cause of having to remain in the ICU at Day 10 for many patients.

Methods

We conducted a retrospective matched case–control study within a 32-bed Australian metropolitan intensive care unit that admits over 2000 patients annually. Approval was obtained from the local Human Research Ethics Committee as a quality assurance project (QA2016110). All adult patients admitted between 1 January 2013 and 31 December 2014, with an ICU length of stay (LOS) > 10 days ("cases"), were identified from the ICU database that reports to the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZCIS APD), and matched to 100 patients admitted within the same time frame with an ICU LOS < 10 days ("controls"). The matching hierarchy was as follows: ANZICS APD diagnostic code, sex, age within 10%, and Acute Physiology and Chronic Health Evaluation (APACHE) III risk of death within 10%. Patients admitted to the ICU for purposes of organ donation were excluded. In the case of patients readmitted to the ICU, only the first ICU episode was eligible for inclusion.

Data collection

We recorded baseline patient data, including age, gender, Charlson comorbidity score, ICU admission source and diagnosis, and presence of treatment limitation on admission. In addition, variables relating to functional status before admission were determined from the medical record, including independence with activities of daily living and Clinical Frailty Scale score.[10] A member of the study team (JD, TB, JN or DM) interrogated the medical record for the entirety of the ICU admission, involving daily data collection until Day 10, and then every third day until ICU discharge or death. Data assessment was calibrated for all four data collectors on five trial medical records before study commencement. We determined daily ICU supports and complications as follows: mechanical ventilation, continuous renal replacement therapy, vasoactive infusions, extracorporeal membrane oxygenation, intra-aortic balloon pump support, non-invasive ventilation, high-flow oxygen requirement > 40 L/min precluding ward discharge, total parenteral nutrition, coma (Glasgow Coma Scale score < 9), critical illness weakness (documented new onset weakness subsequent to ICU admission without brain or spinal cord injury), delirium (documented agitation or fluctuating mental state with administration of quetiapine, olanzapine or dexmedetomidine), or any physiological derangement precluding ward discharge (respiratory rate < 8 or > 30 breaths/min; heart rate < 40 or > 130 beats/min; systolic blood pressure < 90 mmHg).

We also determined the daily underlying need for ICU care as original illness, new sepsis (defined as the commencement of a new antibiotic, plus the presence of two of more of: temperature > 38°C or < 36°C, pulse rate > 90 beats/min, respiratory rate > 20 per min or arterial partial pressure of carbon dioxide level < 32 mmHg, or leukocytosis > 12×10^9/L), surgical complication (anastomotic leak, intra-abdominal or intrathoracic collection, wound dehiscence, unplanned return to the operating theatre), other complication (complication not otherwise defined), or ready for discharge but no ward bed available. We also recorded the last day that the original illness was deemed to persist as the dominant cause for ICU bed requirement (no other underlying need for ICU care, as defined above, supervening). For non-survivors, both the proximate cause of death (neurological, arrhythmia, cardiogenic shock, distributive shock, hypovolaemic shock, hypoxic respiratory failure, metabolic, other) and underlying causes of death (44 options) were chosen using the ICU Deaths Classification and Reason (ICU-DECLARE) tool.[11]

Statistical analysis

All data were initially assessed for normality. Comparisons between persisting critically ill patients and control patients were performed using χ^2 or Fisher exact tests for equal proportion, Student *t* tests for normally distributed data, and Wilcoxon rank-sum otherwise, with results reported as number (%), mean and standard deviation (SD), or median and interquartile range (IQR), respectively.

Daily data (ICU supports or complications and daily underlying need for ICU bed) were compared between groups based on whether an individual variable occurred at least once during a patient's ICU admission, with total aggregate days per variable used for graphical illustration. Cumulative incidence curves were presented for time taken to first requiring an ICU support, complication or need for ICU bed, and compared using log-rank tests. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), and a two-sided $P = 0.05$ indicated statistical significance.

Results

Patient selection, baseline characteristics

We identified 245 patients staying > 10 days from a total of 3874 patients admitted within the study period. From this cohort, given the tightly defined matching criteria, we matched 100 patients with controls. During data collection, 28 pairs were excluded due to some of the paper records being missing, leaving 72 matched pairs (144 patients) available for data analysis. Compared with included patients with PerCI, those patients with missing paper records were more likely to be male, with non-significantly higher APACHE III scores (mean, 92.5 [SD, 34.2] *v* 82.7 [SD, 24.6]; $P = 0.11$) and longer duration of hospital stay (median, 42

Table 1. Baseline demographics and reason for intensive care unit admission: cases versus controls

Baseline characteristics	Cases	Controls	*P*
Total number of patients	72	72	
Age, mean (SD)	60.2 ± 15.5	60.4 ± 16	0.93
Male	46 (64%)	46 (64%)	1.00
APACHE III score, mean (SD)	82.7 ± 24.6	80.9 ± 25.1	0.67
Admission diagnosis			
Sepsis	23 (32%)	23 (32%)	
Head trauma	10 (14%)	10 (14%)	
Other trauma	7 (10%)	7 (10%)	
Subarachnoid haemorrhage	5 (7%)	5 (7%)	
Cardiac arrest	4 (6%)	4 (6%)	1.00
Cardiogenic shock	4 (6%)	4 (6%)	
Cardiac surgery	4 (6%)	4 (6%)	
Intracerebral haemorrhage	4 (6%)	4 (6%)	
Stroke	3 (4%)	3 (4%)	
Coma	1 (1%)	1 (1%)	
Other	7 (10%)	7 (10%)	
Charlson comorbidity score, mean (SD)	3.83 ± 2.41	3.60 ± 2.81	0.59
Limitation of treatment on admission	8 (11%)	10 (14%)	0.61
Clinical Frailty Scale score, median (IQR)	3 (2–4)	3 (2–4)	0.50
Dependence with any ADLs	7 (10%)	9 (13%)	0.64

ADLs = activities of daily living. APACHE = Acute Physiology and Chronic Health Evaluation. IQR = interquartile range. SD = standard deviation.

days [IQR, 21.5–69.5] *v* 30.5 days [IQR, 22–39]; *P* = 0.15), though no difference in time from hospital to ICU admission (online Appendix, table, available at cicm.org.au/journal.php).

The baseline demographics of included patients are shown in Table 1. Corresponding to the matching process, age, gender, admission diagnosis and APACHE III scores were similar between groups. There were also no differences in Charlson comorbidity score, Clinical Frailty Scale score, independence with activities of daily living, readmission to ICU or limitation of medical treatment on admission.

Process of care

Daily reason for remaining in the ICU varied between cases and controls. New sepsis was more than twice as common in persistently critically ill patients (Table 2, Figure 1 and online Appendix, figure 1), peaking at Day 9. Other complications were also more common than in control patients, experienced by nearly half of the persistently critically ill cohort, which increased gradually over the first 10 days (Figure 1, Figure 2 and online Appendix, figure 2).

The original illness persisted as a reason for ICU admission until Day 10 for the majority of cases, falling away steeply beyond that in line with the proportion of patients discharged or deceased. In contrast, very few control patients had new underlying reasons for ICU admission develop beyond their original illness. The final day of the original illness as a cause for ICU admission reflected these graphical trends: median, 10 days (IQR, 7–16) for persistently critically ill patients versus 2 days (IQR, 0–3) for control patients; $P < 0.001$.

There were significant differences in daily ICU supports and complications between groups for all categories (Table 2, Figure 3, Figure 4 and online Appendix, figures 3–5). In particular, a steady increase over time was seen in the number of persistently critically ill patients with delirium, continuous renal replacement therapy and physiological derangement precluding ward discharge, peaking at Days 9, 6 and 13, respectively. The need for and use of mechanical ventilation was the cause for continued ICU stay in only two-thirds of these patients on Day 10 (Figure 3). In contrast, ICU supports in control patients fell away steeply over the first 3–4 days (Figure 4).

Outcomes

LOS in both ICU and hospital was significantly longer in persistently critically ill patients (median, 15.1 days [IQR, 12.2–19.8] *v* 3.0 days (IQR, 1.8–4.3); and 30.5 days (IQR, 22–39) *v* 9.5 days (IQR, 5.5–19.5), respectively; $P < 0.001$ for both), but overall in-ICU and in-hospital mortality rates were similar due to earlier mortality in control patients (Table 2). Cause of death varied between groups, with a greater number of control patients dying of a neurological proximate cause (Table 2), and twice as many patients with PerCI dying of an underlying cause of sepsis with multi-organ failure. Among survivors, patients with PerCI stayed a median 4 days longer in hospital after ICU discharge and were more than twice as likely to be discharged to chronic care or rehabilitation rather than to home (37.5% of patients with PerCI *v* 16.7% of control patients; *P* = 0.01).

Table 2. Intensive care unit (ICU) and hospital outcomes, cause of death, ICU supports and daily reason for ICU: cases versus controls

Characteristics	Cases	Controls	*P*
Total number of patients	72	72	
ICU length of stay (days), median (IQR)	15.1 (12.2–19.8)	3.0 (1.8–4.3)	< 0.01
Hospital length of stay (days), median (IQR)	30.5 (22–39)	9.5 (5.5–19.5)	< 0.01
Time from hospital to ICU admission (days), median (IQR)	0 (0–1.5)	1 (0–2)	0.17
Time from ICU to hospital discharge for survivors (days), median (IQR)	12 (8–24)	8 (4–13)	< 0.01
Mortality in ICU	17 (24%)	21 (29%)	0.34
Mortality in hospital	23 (32%)	25 (35%)	0.73
Discharge destination			
Died	23 (32%)	25 (35%)	0.72
Home	13 (18%)	28 (39%)	0.01
Chronic care/rehabilitation	27 (38%)	12 (17%)	0.01
Other hospital	22 (31%)	20 (28%)	0.60
Proximate cause of death (ICU deceased)			
Neurological	1 (1%)	8 (11%)	0.02
Cardiogenic shock	4 (6%)	4 (6%)	1.00
Distributive shock	5 (7%)	3 (4%)	0.47
Hypoxic respiratory failure	3 (4%)	5 (7%)	0.47
Metabolic	1 (1%)	1 (1%)	1.00
Other	3 (4%)	0 (0%)	0.08
Arrhythmia	0 (0%)	0 (0%)	1.00
Hypovolaemic shock	0 (0%)	0 (0%)	1.00
Underlying cause of death			
Intracerebral haemorrhage	1 (1%)	4 (6%)	0.17
Renal failure	0 (0%)	1 (1%)	0.32
Haemorrhage (non-traumatic)	0 (0%)	2 (3%)	0.15
Sepsis with multi-organ failure	12 (17%)	6 (8%)	0.13
Pneumonia	1 (1%)	1 (1%)	1.00
Other respiratory disease	0 (0%)	1 (1%)	0.32
Traumatic brain injury (primary injury)	1 (1%)	2 (3%)	0.56
Acute myocardial infarction	1 (1%)	2 (3%)	0.56
Other cardiovascular disease	1 (1%)	0 (0%)	0.32
Hepatic failure	0 (0%)	1 (1%)	0.32
Other cause	0 (0%)	1 (1%)	0.32
ICU supports/complications*			
Mechanical ventilation	67 (93%)	49 (68%)	< 0.01
Continuous renal replacement therapy	24 (33%)	7 (10%)	< 0.01
Inotropes/vasoactive infusion	66 (92%)	50 (69%)	< 0.01
IABP/ECMO	16 (22%)	4 (6%)	< 0.01
Non-invasive ventilation	27 (38%)	13 (18%)	< 0.01
Coma	15 (21%)	13 (18%)	0.67
Delirium	27 (38%)	7 (10%)	< 0.01
Total parenteral nutrition	10 (14%)	2 (3%)	0.02
ICU acquired weakness	11 (15%)	0 (0%)	< 0.01

(*Continues*)

Table 2. Continued

Characteristics	Cases	Controls	*P*
Physiological derangement	60 (83%)	34 (47%)	< 0.01
High flow oxygen therapy	24 (33%)	12 (17%)	0.02
Daily reason for ICU bed*			
New sepsis	38 (53%)	17 (24%)	< 0.01
Surgical complication	14 (19%)	10 (14%)	0.35
Other complication	32 (44%)	10 (14%)	< 0.01
No ward bed available	8 (11%)	3 (4%)	0.12
Last day of original illness, median (IQR)	10 (7–16)	2 (0–3)	< 0.01

ECMO = extracorporeal membrane oxygenation. IABP = intra-aortic balloon pump. IQR = interquartile range. * Each patient could have ≥ 1 ICU support, complication or daily reason for ICU bed.

Discussion

Key findings

In this retrospective matched case–control study of 144 patients, we found that patients with a diagnosis of PerCI had a long duration of hospitalisation and were more than twice as likely to be discharged to rehabilitation or institutional care. Persistently critically ill patients were more likely to require ICU supports and to develop ICU-acquired weakness or delirium. New sepsis was more than twice as common, with more patients with PerCI dying of sepsis with multi-organ failure. Moreover, the original illness was no longer a cause for ICU admission at a median 10 days, at which time point more than a third of patients with PerCI remained in the ICU because of reasons and forms of support that did not include mechanical ventilation. We found no significant differences between patients with PerCI and control patients in frailty or disability before onset of illness.

Relationship to prior literature

We observed a high mortality rate for patients with PerCI (32%), a value comparable with the 29% pooled mortality rate of over 12 000 patients across 29 trials in a meta-analysis of prolonged mechanical ventilation,[4] the 24% mortality rate of almost 3000 Canadian patients with PerCI,[5] and the 25% mortality rate in the population of over 50 000 patients with PerCI from 182 ICUs across Australian and New Zealand.[6] The rate of discharge to institutional care was higher than the 17.5% rate in the large Australian and New Zealand study above, possibly explained by the high number of patients with neurological injury in our cohort.[6] We found no differences between patients with PerCI and control patients in the comorbidity score, also in contrast to the above study,[6] perhaps related to differences in casemix. We also observed no significant differences in frailty status and activities of daily living before onset of illness, which are the first report of frailty, function and disability in PerCI in any population.

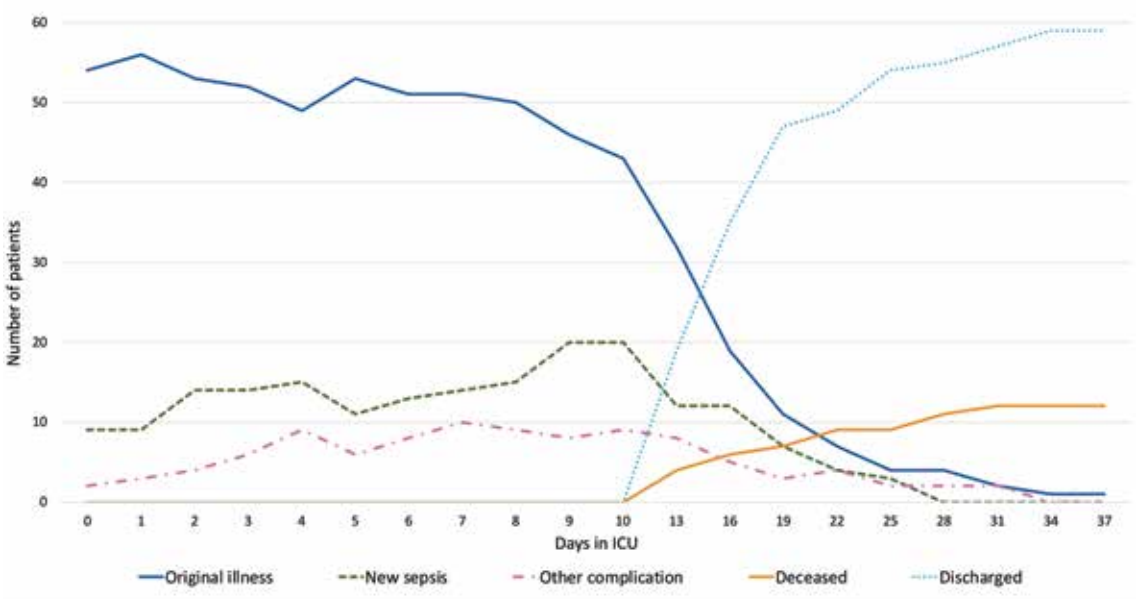
We found that the original illness leading to ICU admission was no longer the dominant cause for continued ICU stay at a median 10 days — a similar transition point for PerCI as reported previously.[5,6] Our findings also align with the proposed timing and definition of PerCI found in a survey of over 100 ICU clinicians (10 days).[1] The emergence of new sepsis in our cohort was maximal at Day 9 and more than twice as common as in control patients. Thus, ICU onset sepsis is likely to be one of the most important contributing complications. This finding concurs with recent work on the link between sepsis, prolonged critical illness, and the theory of "persistent inflammation-immunosuppression and catabolism syndrome".[12]

This study also provides insights into the association between ICU supports and PerCI. It shows that, as hypothesised, the need for mechanical ventilation as the reason for remaining in the ICU does not apply to many patients. Thus, previous literature that studied chronic critical illness using the need for mechanical ventilation as its identifier would have missed a large proportion of persistently critically ill patients.[4,13] Delirium also emerged as an important reason for continued ICU care. Our findings on delirium align with a previous study, describing a delirium prevalence of 46% in a cohort of 203 chronically critically ill patients.[14] Future studies should explore whether factors predisposing to delirium (eg, benzodiazepine use) are more common in patients who develop PerCI.

Implications of the study findings

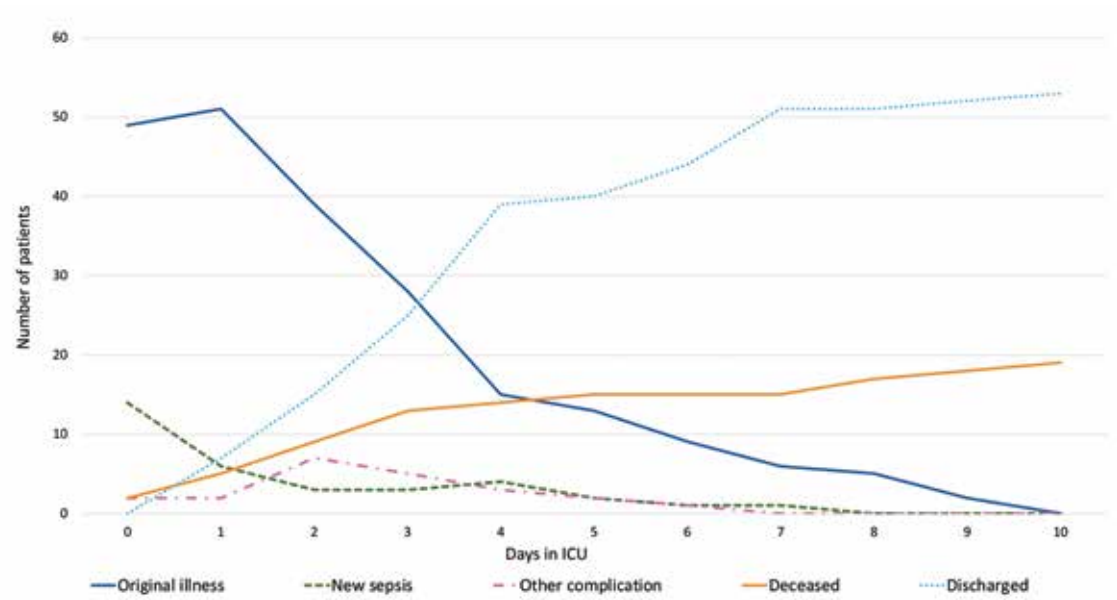
The findings of this study imply that, in line with other recent epidemiologically derived definitions, PerCI develops

Figure 1. Underlying cause for intensive care unit (ICU) admission in cases, demonstrating persistence of the original illness until 10 days for the majority of patients — new sepsis also increased over time*



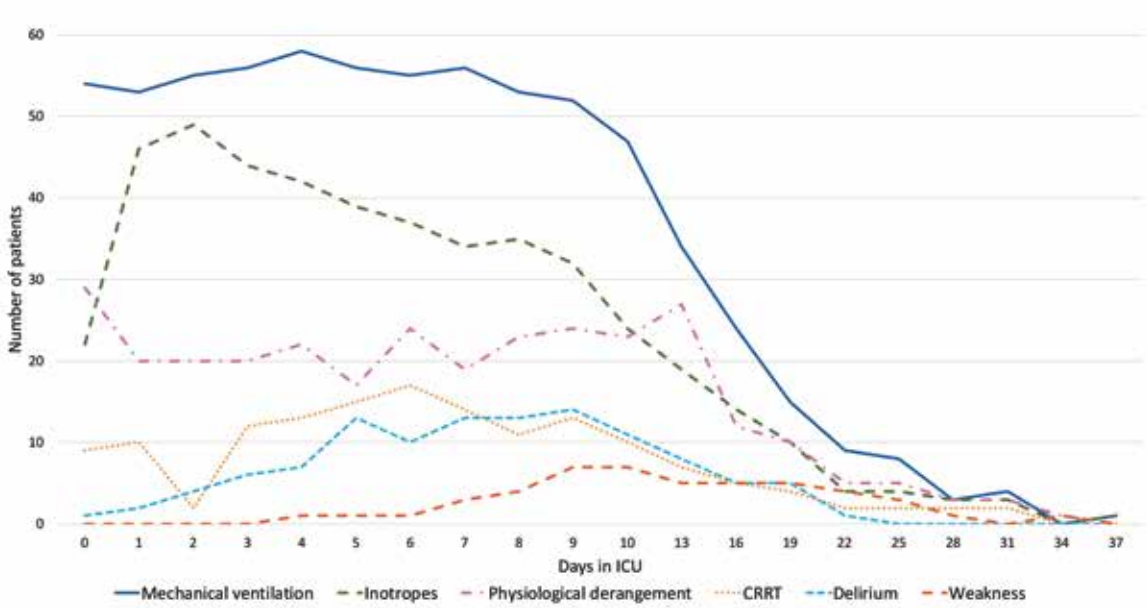
* Initial new sepsis cases represent patients admitted from the ward with new onset sepsis resulting in ICU admission. Surgical complications not shown due to low numbers of affected patients.

Figure 2. Underlying cause for intensive care unit (ICU) admission in control patients showing rapid resolution of the original illness and few other reasons for ICU admission*



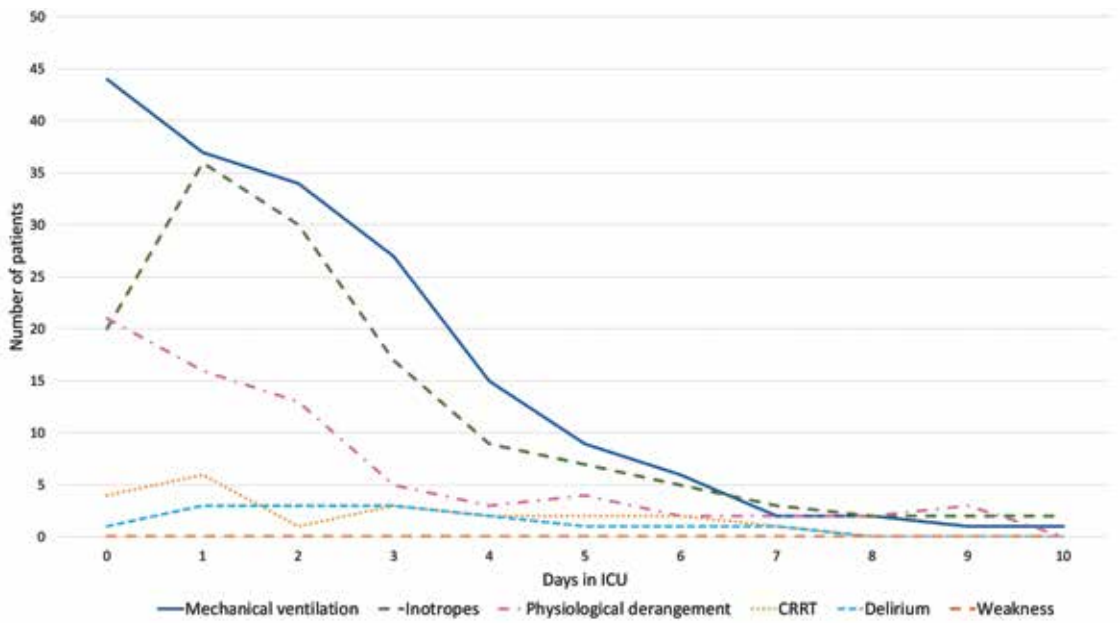
* Initial new sepsis cases represent patients admitted from the ward with new onset sepsis resulting in ICU admission. Surgical complications not shown due to low numbers of affected patients.

Figure 3. Daily intensive care unit (ICU) supports in cases, demonstrating an increase over time in delirium, continuous renal replacement therapy (CRRT), and physiological derangement (peaking at Days 9, 6 and 13, respectively). Mechanical ventilation was a cause for continued ICU stay in only two-thirds of patients at Day 10*



* Non-invasive ventilation, physiological derangement, coma, high flow oxygen, and total parenteral nutrition not displayed due to low numbers of patients.

Figure 4. Daily intensive care unit (ICU) supports in control patients showing a steep reduction over time for all supports over the first 4 days of ICU admission*



CRRT = continuous renal replacement therapy. * Non-invasive ventilation, physiological derangement, coma, high flow oxygen and total parenteral nutrition not displayed due to low numbers of patients.

at a median 10 days. Moreover, they imply that there may be common factors associated with PerCI, including sepsis, which may play an important aetiological role.[15] These results imply that prior definitions such as the requirement for prolonged mechanical ventilation may miss a large proportion of patients with PerCI. A final, provocative finding from our study is insight into the cause of death in persistently critically ill patients. The association (non-statistically significant) of more deaths due to sepsis with multi-organ failure in patients with PerCI is in keeping with the greater number of new sepsis diagnoses in this group, although this finding is in need of confirmation in future studies. Follow-up research should also examine whether specific nosocomial infections are more common in patients with PerCI (eg, ventilator-associated pneumonia). The difference in early neurological deaths in matched control patients was likely due to the inclusion of patients with traumatic brain injury, in whom both early mortality and significantly prolonged ICU stay are common.

Strengths and limitations

Strengths of this study include comprehensive daily data from interrogation of the medical record, providing a granularity not present in prior database studies, and the broad spectrum of admission diagnoses represented, thus enhancing the validity of our findings. Further strengths include utilisation of the validated ICU-DECLARE tool for determining cause of death, and inclusion of baseline demographic factors such as Charlson comorbidity and clinical frailty scores. Limitations include the single-centre, retrospective design, which may diminish external validity and increase the risk of bias. The patient cohort, however, was representative of that managed in a typical tertiary ICU, was well matched with controls, and assessment was applied to about 1000 ICU days, supporting our primary hypothesis and providing a uniquely comprehensive view of PerCI. A limitation was the exclusion of 28 pairs from analysis due to missing paper records, with some baseline differences. We consider it unlikely, however, for this to have decreased the magnitude of our findings. In fact, exclusion of these overall sicker patients may have biased our results away from the true impact of PerCI. Due to the nature of data collection, data assessors were not blinded. This could have been improved by chart interrogation without knowing which day of ICU stay was under consideration; however, due to the nature of longitudinal history recording, we did not consider this logistically possible. Although data assessors could potentially be biased, we consider this unlikely because of both the strict definitions of variables, as described above, and the requirement to select an alternate reason for remaining in the ICU should the original illness be deemed to be no longer applicable. Although data collection was calibrated before study commencement, dual-record interrogation with assessment of inter-rater agreement may have improved internal validity. We also deliberately did not exclude control patients who died within the first 10 days of ICU admission and, thus, were not able to develop PerCI. Exclusion of these patients would have biased our findings away from sicker control patients, potentially leading to a less comparable control cohort. Furthermore, factors in the day-to-day processes of care, which were potentially associated with death in control patients (versus factors influencing development of PerCI), would have been lost. We also did not follow up patients after ICU discharge, thus, more subtle complications (eg, delirium or sepsis, although not severe enough to require ICU readmission) may have been missed. We could have improved the power of our analysis by broadened matching criteria to increase the number of control patients available; for example, a ratio of 1:2 or 1:3 patients; however, this would have necessitated a poorer match between cases and controls. Examination of a larger patient cohort, perhaps using propensity scoring, may have improved estimates around some endpoints, but the granularity of day-to-day data interrogation would have been lost. All prior large studies of PerCI have used a cohort study design, useful in examining the association of exposures of interest with the development of PerCI, but unable to examine the daily nuances of the ICU course of individual patients. As such, our study represents a novel approach to exploring this condition with unique insights.

Conclusion

We have found in a retrospective matched case–control study that persistently critically ill patients were more likely to develop new sepsis, delirium and ICU-acquired weakness, and that these factors appear more important than baseline comorbidities, frailty or independence before ICU admission. Moreover, we found that these patients transition to reasons for ICU admission other than the original illness at a median 10 days; ICU-acquired sepsis was common at this transition. Finally, we found that, as hypothesised, the need for extended mechanical ventilation failed to capture close to a third of patients with PerCI, implying that previous studies based on such mechanical support would have failed to identify a large segment of this population. By helping to understand the natural history of PerCI, these findings may provide the necessary epidemiological background for trials aimed at preventing or attenuating the consequence of this condition.

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Competing interests

None declared.

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