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Persistent Critical Illness and Long-Term Outcomes in Patients With COVID-19: A Multicenter Retrospective Cohort Study

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OBJECTIVES: A nontrivial number of patients in ICUs experience persistent critical illness (PerCI), a phenomenon in which features of the ICU course more consistently predict mortality than the initial indication for admission. We aimed to describe PerCI among patients with critical illness caused by COVID-19, and these patients' short- and long-term outcomes.

DESIGN: Multicenter retrospective cohort study.

SETTING: Australian and New Zealand Intensive Care Society Adult Patient Database of 114 Australian ICUs between January 1, 2020, and March 31, 2022.

PATIENTS: Patients 16 years old or older with COVID-19, and a documented ICU length of stay.

EXPOSURE: The presence of PerCI, defined as an ICU length of stay greater than or equal to 10 days.

MEASUREMENTS: We compared the survival time up to 2 years from ICU admission using time-varying robust-variance estimated Cox proportional hazards models. We further investigated the impact of PerCI in subgroups of patients, stratifying based on whether they survived their initial hospitalization.

MAIN RESULTS: We included 4961 patients in the final analysis, and 882 patients (17.8%) had PerCI. ICU mortality was 23.4% in patients with PerCI and 6.5% in those without PerCI. Patients with PerCI had lower 2-year (70.9% [95% CI, 67.9–73.9%] vs. 86.1% [95% CI, 85.0–87.1%]; $p < 0.001$) survival rates compared with patients without PerCI. Patients with PerCI had higher mortality (adjusted hazards ratio: 1.734; 95% CI, 1.388–2.168); this was consistent across several sensitivity analyses. When analyzed as a nonlinear predictor, the hazards of mortality were inconsistent up until 10 days, before plateauing.

CONCLUSIONS: In this multicenter retrospective observational study patients with PerCI tended to have poorer short-term and long-term outcomes. However, the hazards of mortality plateaued beyond the first 10 days of ICU stay. Further studies should investigate predictors of developing PerCI, to better prognosticate long-term outcomes.

KEYWORDS: Australia and New Zealand Intensive Care Society Adult Patient Database; COVID-19; pandemic; persistent critical illness

Patients admitted to an ICU account for a small proportion of people, but consume a large proportion of resources (1). With time, some patients experience a phenomenon in which features of the ICU course more consistently predict mortality than the patient's initial indication and disease severity on ICU admission. This is also known as persistent critical illness (PerCI), where the antecedent characteristics, rather than the primary pathology, become driving factors in a patient's outcome (2, 3). Numerous large observational studies have been performed in multiple countries and have identified

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KEY POINTS

Question: What is the association between persistent critical illness (PerCI) and long-term outcomes in patients with COVID-19 requiring ICU admission in Australia?

Findings: In this multicenter retrospective cohort study, we found that PerCI was significantly associated with poorer long-term outcomes in patients admitted to the ICU with COVID-19; when analyzed as a nonlinear variable, the patients who stayed in the ICU for more than 10 days the hazards of mortality plateaued.

Meaning: PerCI is an important predictor of not only short- but long-term mortality in patients with COVID-19.

that this point mostly occurs within the second week of ICU stay (days 9–11) but can range between day 5 and day 22 (4–8). Approximately 5–35% of patients admitted to ICU develop PerCI (4–8). The impact of PerCI has been documented previously: patients with PerCI consume more resources, have a higher mortality rate, and are more likely to be discharged to an intermediate long-term care facility rather than home (4, 9).

However, data regarding the impact of PerCI in patients with COVID-19 are sparse. Patients admitted to the ICU with COVID-19 may suffer from respiratory and multiple organ failure during their ICU stay and may require increasing life support with poor short-term outcomes (10–13). As such, it is important to risk-stratify this population and identify which patients are more likely to have poor outcomes. With this in mind, we performed a multicenter retrospective study of the Australia and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD), analyzing the effect of PerCI on long-term outcomes in patients with COVID-19.

MATERIALS AND METHODS

Study Design and Study Participants

The study was approved as a low-risk project by the Human Research and Ethics Committee of The Alfred Hospital (project number 413/19, "BMI and frailty in Critical Illness," approved November 1, 2022). All research procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. This was an observational cohort study of deidentified patient and institutional data. There were no interventions on patients. This was unfunded research undertaken by the investigators. We adhered to the Strengthening The Reporting of OBservational studies in Epidemiology statement (**Supplementary Table 1**, http://links.lww.com/CCX/B317), and conducted a retrospective multicenter observational cohort study. We included all patients 16 years old or older admitted to an ICU in Australia between January 1, 2020, and March 31, 2022 with COVID-19, a documented length of stay in the ICU and clinical frailty scale (CFS). Patients with frailty are defined as those with CFS greater than or equal to 5 (14). We only included the first hospital admission during the study period. We excluded patients who were transferred from another ICU or admitted for palliation or organ donation.

Data Sources and Collection

We extracted data from the ANZICS-APD, a binational clinical quality registry dataset, collected by the ANZICS Centre for Outcomes and Resources Evaluation, which contains information on all admissions to 98% of adult ICUs in Australia. We extracted data on patient demographics (age, sex, comorbidities, ethnicity, ICU admission source, smoking status), frailty status using the CFS, body mass index (based on the patient's weight and height, which could have been estimated at ICU admission), ICU organ supports (invasive mechanical ventilation, noninvasive ventilation, vasopressors, extracorporeal membrane oxygenation, and/or renal replacement therapy), ICU and hospital mortality, ICU and hospital length of stay, and discharge destinations (home, chronic care facility, or rehabilitation). Data are collected using a standardized data dictionary (15). Data collectors receive regular training and quality assurance reviews. In addition, regular automated data checks further ensure the validity of recorded data (16). Apart from each patient's demographic details, the registry also captures their diagnostic, biochemical, physiologic, and chronic health parameters from the first 24 hours of ICU admission to calculate illness severity scores, such as Acute

Physiology and Chronic Health Evaluation II and III, Sequential Organ Failure Assessment (SOFA) on day 1 of ICU admission, and Australian and New Zealand risk of death (ANZROD) scores. The definitions are described in the ANZICS-APD data dictionary (15). We then matched deidentified ICU admission episodes listed in the ANZICS-APD Registry with the National Death Index using an encoded linkage key.

Study Outcomes

The primary outcome was a survival time of up to 3 years from ICU admission. Secondary outcomes included overall survival at 1 and 2 years of follow-up, ICU and hospital mortality, ICU and hospital length of stays, and discharge destinations.

Statistical Analysis

We summarized categorical data using counts and percentages, and continuous data using mean ± SD or median (interquartile range) as appropriate. We compared between groups using the Chi-square, Student *t*, or log-rank tests as appropriate. We administratively censored time-to-event data on March 31, 2022 to ensure that there was at least 1-day follow-up for all patients. We estimated overall survival over time using the Kaplan-Meier method (17). To account for confounders, we analyzed survival times up to 2 years using a time-varying Cox proportional hazards model and adjusted for age, sex, comorbidities, SOFA score on day 1 of iCU admission, hospital type and jurisdiction, and the presence of frailty. We report adjusted hazards ratios (HRs) and 95% CIs. Given that patients must first survive for 10 days in the ICU to develop PerCI, there is a risk of immortal time bias. As such, we modeled the ICU length of stay as a time-varying coefficient (18). As it is likely that estimates cluster within centers and vary between them, we used robust sandwich-type estimators to estimate the standard errors (19).

We conducted several sensitivity analyses. First, we adjusted for a different pool of confounders, substituting SOFA scores, comorbidities, and the presence of treatment limitations for the ANZROD score. ANZROD is a highly discriminatory and locally derived prediction model for in-hospital mortality and is used for benchmarking ICU performance in Australia and New Zealand (20, 21). Second, we substituted the presence of PerCI with the length of stay, modeling it as a continuous nonlinear variable. Third, to assess the robustness of the primary analysis, we performed a stratified Cox regression and specified PerCI as a stratum term which allowed us to relax the proportional hazards assumption. We performed data analysis using R4.2.2 (The R Foundation, Boston, MA) and IBM SPSS, Version 27 (Armonk, NY). We used a two-sided *p* value of less than 0.05 to indicate statistical significance.

We also conducted three post hoc analyses. First, we analyzed the effect of PerCI on long-term outcomes based on "waves" of COVID-19. We categorized the progression of COVID-19 in Australia based on previously published data and defined the first wave as patients admitted up until June 2020, the second wave as patients admitted between July 2020 and June 2021, and the third wave as patients admitted after July 2021. Second, we analyzed the effect of PerCI stratifying based on the presence of treatment limitations. We investigated for heterogeneity between each subgroup by introducing an interaction term. Third, we changed the point of survivorship from the time of ICU admission to the time of ICU discharge as an exploratory analysis.

RESULTS

Within the study period, 5770 patients were admitted to ICUs in Australia with a diagnosis of COVID-19. Of these, 4961 patients from 114 ICUs were eligible for analysis after applying our inclusion and exclusion criteria (**Supplementary Fig. 1** http://links.lww.com/CCX/B317). There were some differences in baseline characteristics and comorbidities, illness severity and receipt of ICU support, and survival duration after hospital discharge but the overall ICU and hospital mortality rates and post-ICU hospital length of stay between the patients with and without CFS (**Supplementary Table 2**, http://links.lww.com/CCX/B317). The baseline characteristics, and severity of illness scores of patients with and without PerCI are summarized in **Table 1**. There were no substantial differences in age between both groups of patients (61.4 yr with PerCI vs. 60.5 yr without), but patients with PerCI were more likely to be male (559/882 [66.0%] vs. 1320/4079 [59.5%], $p < 0.001$). Patients with PerCI were more likely to be admitted from a general ward (440/882 [49.9%] vs. 1471/4079 [36.1%]) or other

TABLE 1.
Patient Characteristics and Severity of Illness Scores Between Those With and Without Persistent Critical Illness

Variables	Patients Without PerCI (*n* = 4079)	Patients With PerCI (*n* = 882)	*p*
Male sex	1,320 (59.5%)	559 (66.0%)	< 0.001
Indigenous status	164 (4.0%)	18 (2.0%)	< 0.001
Age (yr)	60.5 (46.8, 72.3)	61.4 (50.3, 70.3)	0.47
Age group			
<65 yr	2,436 (59.7%)	521 (59.1%)	0.72
≥65 yr	1,643 (40.3%)	361 (40.9%)	
Frailty status			
Clinical Frailty Scale score	3 (2, 4)	3 (2, 3)	< 0.001
Patients with frailty (clinical frailty scale 5–8)	802 (19.7%)	112 (12.7%)	< 0.001
Hospital classification			
Public metropolitan	1,227 (30.1%)	241 (27.3%)	< 0.001
Public tertiary	1,907 (46.8%)	578 (65.5%)	
Public rural/regional	795 (19.5%)	51 (5.8%)	
Private	150 (3.7%)	12 (1.4%)	
ICU admission source			
ED	2400 (58.8%)	382 (43.3%)	< 0.001
General ward	1471 (36.1%)	440 (49.9%)	
Other hospital (ED and ICU)	175 (4.3%)	56 (6.3%)	
Other[a]	33 (0.8%)	4 (0.5%)	
Major ICU admission diagnosis			
COVID-19 pneumonitis	2593 (63.6%)	758 (85.9%)	< 0.001
Exacerbation of chronic obstructive pulmonary disease	491 (12.0%)	15 (1.7%)	
Other medical admissions	487 (11.9%)	63 (7.1%)	
Sepsis other than pneumonia	461 (11.3%)	39 (4.4%)	
Cardiac arrest	58 (1.4%)	9 (1.0%)	
Preexisting conditions			
Chronic respiratory condition	678 (16.6%)	60 (6.8%)	< 0.001
Chronic cardiovascular condition	432 (10.6%)	47 (5.3%)	< 0.001
Chronic renal failure	151 (3.7%)	15 (1.7%)	0.003
Chronic liver disease	32 (0.8%)	8 (0.9%)	0.71
Diabetes mellitus	1159 (28.4%)	311 (35.3%)	< 0.001
Immune suppressive therapy	100 (4.5%)	42 (5.0%)	0.60
Lymphoma	27 (0.7%)	7 (0.8%)	0.67
Leukemia	50 (1.2%)	9 (1.0%)	0.61
Cancer without metastasis	162 (4.0%)	22 (2.5%)	0.035
Metastatic cancer	86 (2.1%)	6 (0.7%)	0.004
Obese (body mass index ≥ 30 kg/m^2)	1104 (27.0%)	302 (34.2%)	< 0.001
Pregnant or postpartum	90 (2.2%)	11 (1.2%)	0.040

(*Continued*)

TABLE 1. (*Continued*)

Patient Characteristics and Severity of Illness Scores Between Those With and Without Persistent Critical Illness

Variables	Patients Without PerCI (*n* = 4079)	Patients With PerCI (*n* = 882)	*p*
Miscellaneous			
Delirium in ICU	159 (3.9%)	155 (17.6%)	< 0.001
ICU discharge delay, hr	4.0 (2.0, 7.3)	4.7 (2.2, 8.8)	< 0.001
ICU admission post-medical emergency team call	1078 (26.4%)	332 (37.6%)	< 0.001
Hours in hospital preadmission	8.6 (4.4, 29.5)	13.1 (4.0, 58.5)	< 0.001
Treatment limitations at ICU admission	687 (16.8%)	46 (5.2%)	< 0.001
Cardiac arrest in the 24 hr before ICU admission	58 (1.4%)	9 (1.0%)	0.06
ICU supports			
Noninvasive ventilation	1442 (35.4%)	457 (51.8%)	< 0.001
Mechanical ventilation	812 (19.9%)	700 (79.4%)	< 0.001
Mechanical ventilation on day 1 ICU	662 (16.2%)	416 (47.2%)	< 0.001
Vasopressor and inotropes	1024 (25.1%)	643 (72.9%)	< 0.001
Renal replacement therapy	87 (2.1%)	128 (14.5%)	< 0.001
Extracorporeal membrane oxygenation	13 (0.3%)	51 (5.8%)	< 0.001
Tracheostomy	7 (0.2%)	157 (17.8%)	< 0.001
Acuity of illness			
APACHE II	15 (11, 20)	16 (13, 20)	< 0.001
APACHE III	47 (35, 63)	55 (43, 67)	< 0.001
ANZROD (%)	4.8 (2.2, 11.8)	6.9 (3.5, 14.4)	< 0.001
ANZROD (%)	10.3 (14.4)	11.7 (13.1)	0.27
Sequential Organ Failure Assessment score on day 1 of ICU admission	3 (2, 5)	4 (3, 6)	< 0.001

ANZROD = Australian and New Zealand risk of death, APACHE = Acute Physiology and Chronic Health Evaluation, ED = emergency department, PerCI = persistent critical illness.

[a]Other—direct admits, and admission from operating theater/recovery.

Data are *n* (%), mean [SD] or median (interquartile range).

hospitals (56/882 [6.3%] vs. 175/4079 [4.3%]) than from the emergency department (382/882 [43.3%] vs 2400/4079 [58.8%]) compared with patients without PerCI and were more likely to have COVID-19 pneumonitis (758/882 [85.9%] vs. 2593/4079 [63.6%]). The patients with PerCI also had more comorbidities and required more organ support interventions including noninvasive (457/882 [51.8%] vs. 1442/4079 [35.4%]) and invasive mechanical ventilation (700/882 [79.4%] vs. 812/4079 [19.9%]), tracheostomy (157/882 [17.8%] vs. 7/4079 [0.2%]), vasoactive medications (643/882 [72.9%] vs. 1024/4079 [25.1%]), extracorporeal membrane oxygenation (51/882 [5.8%] vs. 13/4079 [0.3%]), and renal replacement therapy (128/882 [14.5%] vs. 87/4079 [2.1%]).

Primary Outcome

Patients with PerCI had lower 1-year (76.3% [95% CI, 73.5–79.2%] vs. 87.7% [95% CI, 86.7–88.7%]; *p*

TABLE 2.
Unadjusted Primary and Secondary Outcomes Between Patients With and Without Persistent Critical Illness

Variable	Patients Without PerCI (*n* = 4079)	Patients With PerCI (*n* = 882)	*p*
Overall survival at 1 yr	87.7% (86.7–88.7%)	76% (73.5–79.2%)	< 0.001
Overall survival at 2 yr	86.1% (85.0–87.1%)	70.9% (67.9–73.9%)	< 0.001
Survival time (mo)	6.8 (4.6, 13.2)	5.9 (1.1, 7.5)	< 0.001
In-hospital mortality			
ICU mortality overall	267 (6.5%)	207 (23.5%)	< 0.001
Hospital mortality overall	408 (10.0%)	232 (26.3%)	< 0.001
Length of stay			
ICU length of stay overall	2.7 (1.4, 4.8)	16.5 (12.5, 24.7)	< 0.001
Post-ICU length of stay	3.9 (1.2, 7.3)	5.4 (0.0, 13.8)	< 0.001
Hospital length of stay overall	8.3 (4.7, 13.2)	25.1 (18.6, 40.0)	< 0.001
ICU readmission overall	101 (4.6%)	26 (3.1%)	0.07
Discharge destination			
Home discharge overall	2928 (71.8%)	376 (42.6%)	< 0.001
New nursing home discharge overall	30 (0.7%)	5 (0.6%)	0.59
Rehabilitation	79 (1.9%)	101 (11.5%)	< 0.001

PerCI = persistent critical illness.
Data are % (95% CI), *n* (%), mean [SD] or median (interquartile range).

< 0.001) and 2-year (70.9% [95% CI, 67.9–73.9%] vs. 86.1% [95% CI, 85.0–87.1%]; $p < 0.001$) survival rates compared with patients without PerCI (**Table 2**). PerCI was associated with mortality (adjusted HR: 1.734; 95% CI, 1.388–2.168; **Fig. 1**; **Table 3**). The effect estimate remained similar across the sensitivity analyses, including consideration of a different pool of confounders (adjusted HR: 1.673; 95% CI, 1.315–2.129; **Supplementary Table 3**, http://links.lww.com/CCX/B317). The covariates in the stratified model were also similar to those in the Cox proportional hazards model (**Supplementary Table 4**, http://links.lww.com/CCX/B317).

When modeled as a continuous nonlinear variable, there was no consistent or significant association between survival with time until ten days in the ICU, following which there was an association with lower survival up to 2 years when compared with shorter durations of ICU stay. In addition, beyond the first 10 days, the increased hazard of death trend stayed relatively constant but was not statistically significant (**Fig. 2**).

Secondary Outcomes

Patients with PerCI had higher ICU mortality (23.5% vs. 6.5%) and in-hospital mortality (26.3% vs. 10.0%) compared with those without PerCI (Table 3). In addition, the length of stay in the ICU (16.5 d [12.5–24.7] vs. 3.4 d [1.4–4.8] ; $p < 0.001$) and hospital (25.1 d [18.7–40.0] vs. 8.3 [4.7–13.2]; $p < 0.001$) was longer in patients with PerCI. Furthermore, the post-ICU length of hospital stay was longer in patients with PerCI (5.4 d [0.0–13.8] vs. 3.9 d [1.2–7.3]; $p < 0.001$). The number of bed-days consumed by patients with PerCI was higher than those without PerCI (19,727.6 d [22.4 d per patient] vs. 13,723.4 d [3.4 d per patient]; $p < 0.001$). Among survivors, patients with PerCI were less likely to be discharged back to their usual residence (79.8% vs. 57.8%; $p < 0.001$).

Post hoc Analyses

When analyzing the effect of PerCI based on waves, we found that there were no significant differences in the association between PerCI and mortality in wave

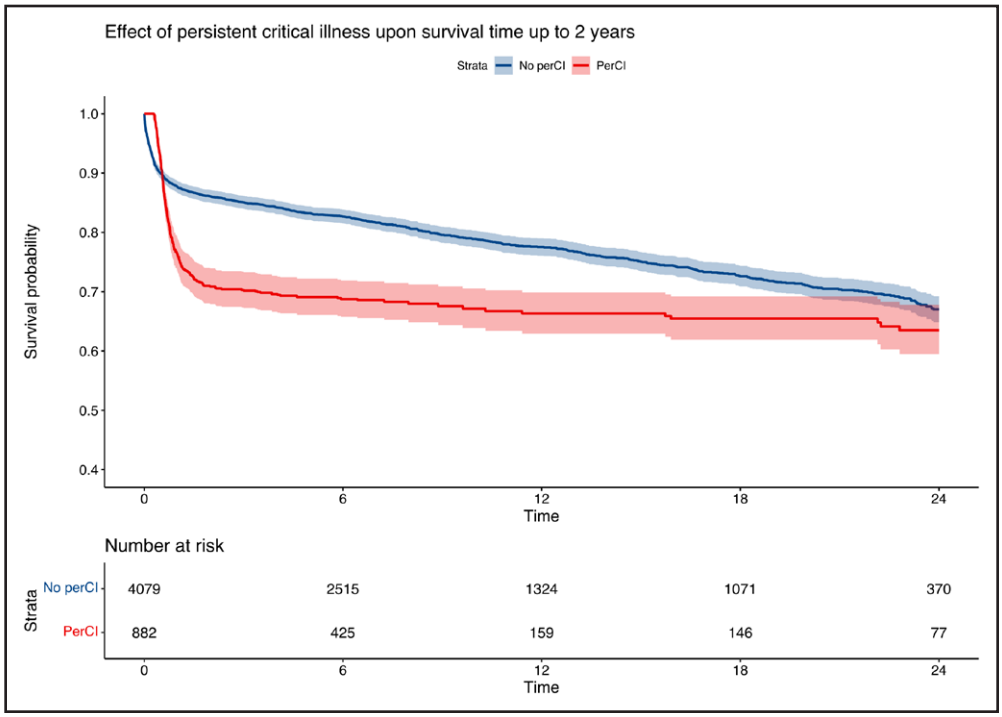

Figure 1. Association between persistent critical illness (perCI) and survival time up to 2 years in patients with COVID-19.

1 (1149 patients; HR: 0.679; 95% CI, 0.378–1.220) and wave 2 (886 patients; HR: 1.360; 95% CI, 0.586–3.155; interaction p = 0.52). However, the impact of PerCI in wave 3 was significantly greater (2926 patients; HR: 2.087; 95% CI, 1.746–2.495) compared with wave 2 (interaction p value, **Supplementary Table 5**, http://links.lww.com/CCX/B317). When analyzing the association between PerCI and mortality based on the presence of treatment limitations, we found that PerCI was associated with similar effects among patients with treatment limitations (HR: 1.383; 95% CI, 0.806–2.374) compared with those without (HR: 2.122; 95% CI, 1.719–2.620; interaction p = 0.06; **Supplementary Table 6**, http://links.lww.com/CCX/B317 and **Supplementary Fig. 2**, http://links.lww.com/CCX/B317). There was no significant association between PerCI and survivorship from ICU discharge among survivors (HR: 1.255; 95% CI, 0.845–1.863; **Supplementary Table 7**, http://links.lww.com/CCX/B317).

DISCUSSION

In this multicenter retrospective cohort study of 4961 COVID-19 patients admitted to Australian ICUs, we found that PerCI was associated with poorer outcomes. In addition, we found that ICU length of stay had an inconsistent association with outcomes before 10 days; beyond this, the hazards of mortality plateaued without any major increase in risk for durations of stay in ICU longer than 10 days. Patients with PerCI were also less likely to be discharged back to their usual residence and had higher use of ICU-bed days, indicating an increased need for healthcare resources.

We found that 18% of patients developed PerCI, and consumed about 60% of the total bed-days. This appears higher than before COVID-19. Pre-COVID-19 only 3–10% of patients in the ICU had PerCI and consumed up to one-third of resources (5, 22). During COVID-19 up to 50% of patients had PerCI and used 80.6% of bed days (23). There are several reasons which may account for the difference in prevalence of PerCI between COVID-19 and non-COVID-19 populations. First, patients with COVID-19 may have received more ICU support, which is associated with longer ICU stays, resulting in longer stays in the ICU compared with patients without COVID-19. Second, the lack of treatment limitations may be associated with prolonged care in the ICU. Patients admitted to a hospital after 2020 were less likely to have treatment limitations, although COVID-19 itself was not associated with the lack of treatment limitations (24, 25). It is possible that goals of care may not have been explored in these patients. Yet, it is equally possible that patients with clear treatment limitations avoided admission to the ICU, hence inflating the proportion of patients without treatment limitations in the ICU. Finally, secondary infections may be more common in patients with severe COVID-19, and these mechanistically could have resulted in longer critical illness. This may be attributed to the disease itself, or the interventions used to treat severe COVID-19, including corticosteroids

TABLE 3.

Cox Proportional Hazards Regression Analysis, for up to 2-Year Survival, Based on the Persistent Critical Illness Status Adjusted for Sequential Organ Failure Assessment on day 1 of ICU admission, Male Sex, Frailty, Comorbidities, Hospital Type, and Jurisdiction for All Patients

Predictor	HR (95% CI) Reference	*p*
Persistent critical illness		
Patients without PerCI	Reference	
Patients with PerCI	1.734 (1.388–2.168)	< 0.001
Time-varying variable for ICU days	0.998 (0.992–1.003)	0.42
Demographics		
Male sex	1.131 (1.011–1.266)	0.031
Age	1.042 (1.034–1.050)	< 0.001
Frailty (clinical frailty scale, per increase of 1)	1.596 (1.368–1.863)	< 0.001
Comorbidities		
Chronic respiratory condition	1.476 (1.206–1.805)	< 0.001
Chronic cardiovascular condition	0.909 (0.728–1.135)	0.40
Chronic renal failure	1.026 (0.793–1.326)	0.85
Chronic liver disease	1.569 (0.897–2.746)	0.11
Diabetes mellitus	1.079 (0.933–1.248)	0.31
Metastatic cancer	2.256 (1.819–2.796)	< 0.001
Patient factors		
Sequential Organ Failure Assessment score on day 1 of ICU admission (per increase of 1)	1.141 (1.109–1.174)	< 0.001
Hospital classification		
Metropolitan	Reference	
Private	0.792 (0.656–0.957)	0.016
Rural/regional	0.928 (0.774–1.112)	0.42
Tertiary	0.876 (0.707–1.086)	0.23
Jurisdiction		
Australian Capital Territory	Reference	
New South Wales	1.862 (1.292–2.683)	0.001
Northern Territory	1.623 (0.775–3.401)	0.20
Queensland	1.082 (0.627–1.867)	0.78
South Australia	1.081 (0.738–1.583)	0.69
Tasmania	1.231 (0.543–2.789)	0.62
Victoria	1.866 (1.323–2.633)	< 0.001
Western Australia	1.410 (0.595–3.339)	0.44

HR = hazard ratio, PerCI = persistent critical illness.

and immunomodulators, which have been associated with secondary pneumonia (26). It is evident that there exists a complex relationship between resource consumption and ICU bed occupancy rates over time, and this relationship will be critical when planning for future pandemics or waves of COVID-19.

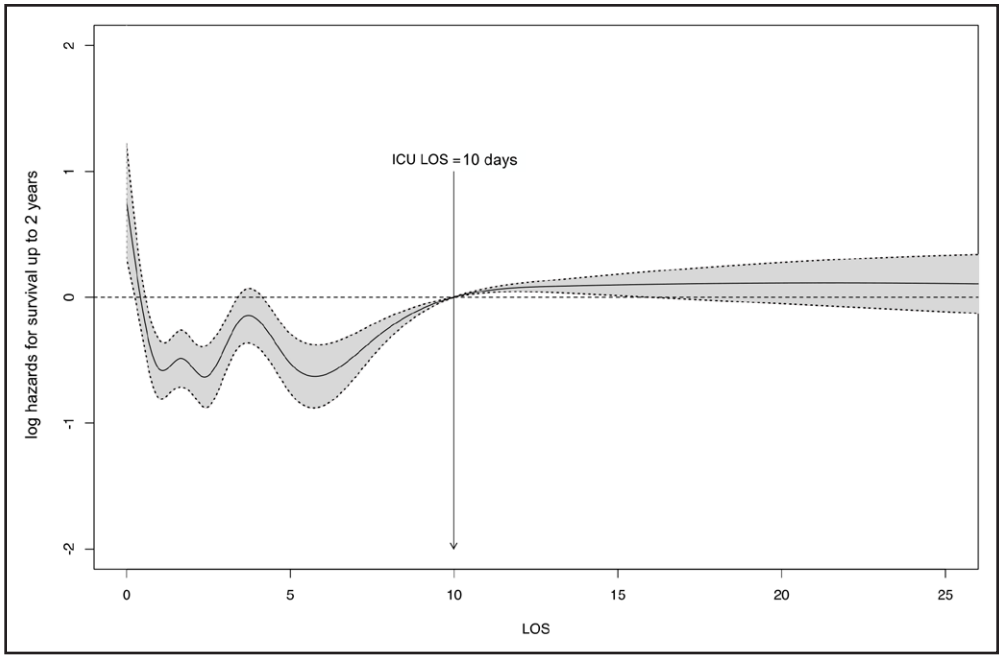

Figure 2. Relationship between ICU length of stay (LOS) and survival time up to 2 years.

Although we found poorer longer-term outcomes in patients with PerCI when modeled as both a categorical and a nonlinear variable, previous studies found no differences in outcomes (27). Two main reasons could account for the discrepancies above. First, there is a possibility of immortal time bias (18). As patients must first survive a certain amount of time (10 d in our study) to develop PerCI, patients with PerCI are in effect "immortal" for the first 10 days of ICU admission, whereas patients who were censored or died before 10 days would necessarily not have PerCI. This can inflate the survival time for patients with PerCI, which must be accounted for. We used a time-varying Cox model to account for the immortal time bias, which could explain some of the differences in results. Second, a nonlinear model, while accounting for the possible nonlinear nature of other continuous variables, maybe a more accurate representation of PerCI. By definition, PerCI is the timepoint in which the predictive capacity of baseline data exceeds the predictive capacity of ICU data, rather than an arbitrary threshold of a certain duration in the ICU. On average, patients in our study stayed in the ICU for 6.7 days, but this can go as high as 21 days in other countries (23, 28–30). By relaxing the categorical nature of ICU length of stay, a nonlinear regression may more appropriately represent how the ICU length of stay is associated with longer-term outcomes in patients with COVID-19. The profile of patients who develop PerCI may vary over time and place, highlighting the need to reassess resource consumption and ICU admission criteria longitudinally to ensure appropriate resource allocation.

There are several strengths to our study. This study encompasses many ICUs and patients across Australia, which provides a relatively large sample size and precise estimates when deriving the effect of PerCI on outcomes. Using a time-varying Cox model allowed us to adjust for immortal time bias, and the sensitivity analyses lend weight to the primary Cox analysis. In addition, we were able to use robust-variance estimation to account for the intracenter correlation of outcomes in studies, and the significant findings despite more conservative estimates of error suggest robustness in our results. Finally, we were able to investigate the effect of PerCI on longer-term mortality, in particular survival time up to 2 years. This has not been reported in previous studies.

However, we recognize several limitations. As a retrospective observational study, there is a possibility of inaccurate data coding without site-based auditing of diagnostic codes. It is unclear how misclassification, if present, would affect the results of our analysis. Observational data are limited by immortal time bias, and time-varying models may not completely account for this. More modern methods such as temporal propensity scores may mitigate this risk further, but unfortunately, we did not have longitudinal data to estimate this. It is likely that immortal time bias inflates the survival time of patients with PerCI and as such, the association between PerCI and mortality may be larger than we report. In addition, we are only able to draw associations and not causal inferences based on these data. Second, given that PerCI does not necessarily follow an arbitrary threshold of ICU length of stay, and can vary across locations and time, the extent to which PerCI affects outcomes in this study may not

reflect its potential effects in the future, or other locations or countries. As a corollary to this, the threshold for PerCI may vary between patients, and an estimate summarizing this for nearly 5000 patients may not accurately depict how ICU length of stay affects outcomes in individual patients. Third, after discharge, the database did not record any ongoing healthcare needs. As a result, it is challenging to determine the precise association between mortality and PerCI after discharge on long-term discharge destination and frailty in addition to mortality. More importantly, other long-term outcomes including functional status and quality of life metrics are critical in the context of PerCI, but these were not recorded in the ANZICS-APD. Fourth, the results from this dataset cannot be translated to a non-critically ill population. Finally, mortality rates from the COVID-19 pandemic in Australia are considerably lower than the global average (31), which may suggest that magnitude of COVID-19 is largely under control. Therefore, the results may not be generalizable in resource-constrained healthcare systems.

CONCLUSIONS

In this multicenter retrospective observational study patients with PerCI tended to have poorer short-term and long-term outcomes. The hazards of mortality plateaued beyond the first 10 days of ICU stay. Patients with PerCI were also less likely to be discharged back to their usual residence and consumed significantly more resources than patients without PerCI.

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The study was approved as a low-risk project by the Human Research and Ethics Committee of The Alfred Hospital (project number 413/19, "BMI and Frailty in Critical Illness," approved November 1, 2022), All research procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. This was an observational cohort study of deidentified patient and institutional data. There were no interventions on patients. This was unfunded research undertaken by the investigators.

The data dictionary and Australia and New Zealand Intensive Care Society (ANZICS) Adult Patient Database policies are available online. The participant data collected for this study are available, as a limited dataset, to member centers conditional on approval from the ANZICS Centre for Outcome and Resource Evaluation Management Committee, but it is not publicly available.

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