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Procalcitonin concentrations as a predictor of unexpected readmission and mortality after intensive care unit discharge: A retrospective cohort study☆,☆☆

George Zhou, MBBS [a,*], Kwok M. Ho, FCICM, MPH, PhD [a,b,c]

[a] Department of Intensive Care Medicine, Royal Perth Hospital, Perth, WA 6000, Australia
[b] School of Population Health, University of Western Australia, Perth, WA 6000, Australia
[c] School of Veterinary and Life Sciences, Murdoch University, Perth, 6150, Australia

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ABSTRACT

Procalcitonin (PCT) has been used to guide treatment in critically ill patients with sepsis, but whether PCT at intensive care unit (ICU) discharge can stratify risks of post-ICU readmission or mortality is unknown. This cohort study compared the ability of PCT with C-reactive protein (CRP) in predicting unexpected adverse post-ICU events. Of the 1877 patients admitted to the multidisciplinary ICU between 1 April 2012 and 31 March 2014, 1653 (88.1%) were discharged without treatment limitations. A total of 71 (4.3%) were readmitted and 18 patients (1%) died unexpectedly after ICU discharge during the same hospitalization. Both PCT (0.6 vs 0.4 μg/L, $P = .002$) and a high CRP concentration >100 mg/L (58% vs 41%, $P = .004$) at ICU discharge were associated with an increased risk of adverse post-ICU events in the univariate analyses; however, the ability of PCT to discriminate between patients with and without adverse post-ICU outcomes was limited (area under the receiver operating characteristic curve = 0.61; 95% confidence interval, 0.55-0.66). In the multivariable analysis, only a high CRP concentration (odds ratio, 1.92; 95% confidence interval, 1.12-3.11; $P = .008$) was associated with an increased adverse post-ICU events. Elevated PCT concentration at ICU discharge was inadequate in its predictive ability to guide ICU discharge.

1. Introduction

Unexpected readmission and mortality after intensive care unit (ICU) discharge are potentially preventable adverse outcomes after apparently successful treatment of critical illness. Despite significant improvement in overall outcomes of critically ill patients in the past 2 decades, post-ICU readmission and mortality rates remain high and exceed 4% in many institutions [1]. Post-ICU readmission and mortality are intrinsically interrelated, with a 4-fold increase in hospital mortality for patients who are readmitted [2–6]. These 2 adverse outcomes after ICU discharge also share similar risk factors, with patients with chronic health conditions and unstable physiological parameters at ICU discharge being most vulnerable to these adverse events after ICU discharge [7,8]. Although some prognostic scores have been shown to predict post-ICU readmission and mortality [9,10], many of these scores are difficult to estimate at the bedside, and as such, most practicing clinicians still rely on subjective assessment of their patients to determine whether their patients are suitable for ICU discharge [11].

Recurrent or persistent infection and inflammation may play a role in leading to unexpected readmission or mortality after ICU discharge. This hypothesis is supported by the fact that inflammatory markers such as C-reactive protein (CRP) and white blood cell (WBC) count at ICU discharge were more likely to be elevated among those who were subsequently readmitted compared with those without readmission [11–15]. Similarly, eosinopenia, a marker of bacterial infection, at ICU discharge had also been reported to be more common among those who experienced post-ICU readmission or mortality compared with those without such adverse events [16]. Procalcitonin (PCT) has a shorter half-life and is more specific in its association with infection than CRP [17,18]. Indeed, normalization of PCT has been suggested to be useful in guiding cessation of antibiotic for patients with infection [19–21]. Recently, a high PCT concentration at ICU discharge was also reported to be associated with an increased risk of unexpected mortality after ICU discharge in a small cohort study [22].

We hypothesized that an elevated PCT concentration at ICU discharge is a reliable predictor for adverse outcomes after ICU discharge and conducted a cohort study to assess whether PCT concentration at ICU discharge is a better predictor for post-ICU readmission and mortality than CRP concentrations. Specifically, we assessed whether measuring these inflammatory markers at ICU discharge was more predictive

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* Corresponding author at: Department of Intensive Care Medicine, Royal Perth Hospital, Perth, WA 6000, Australia.
E-mail address: george.zhi.zhou@gmail.com (G. Zhou).

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of post-ICU readmission or mortality in patients admitted to the ICU with an infective cause.

2. Materials and methods

This was a single-center retrospective cohort study. The Fremantle Hospital Quality and Safety Unit was approached regarding ethics approval, and this study was approved as a Quality Improvement project without requiring formal ethics approval due to use of existing administrative and laboratory data only. Outcome and laboratory data of all patients who were admitted to the ICU between April 1, 2012, and March 31, 2014, were retrieved for this study. Fremantle Hospital ICU was a 12-bed multidisciplinary ICU admitting patients from all medical specialties and most surgical specialties, including cardiothoracic surgery. Patients after organ transplantation, multiple trauma, neurosurgery, and burns were not admitted to this ICU. This ICU had a policy of measuring daily PCT concentrations for all patients. PCT was measured by BRAHMS PCT ECLIA (Roche Diagnostics, Switzerland; normal range, <0.05 μg/L). CRP was measured by an immunoenzyme analyzer (Hitachi 917, Tokyo, Japan; normal range, <5 mg/L). During the study period, patients were discharged from the ICU once the patients did not require any organ support and were deemed to be safe to be discharged by the duty intensivists. No standardized objective criteria including PCT concentrations or prognostic scores were used to determine ICU discharge.

The predictors for adverse events after ICU discharge assessed in this study included PCT and CRP concentrations, eosinopenia (or undetectable eosinophil count $<10/mm^3$), and WBC count on the day of ICU admission and discharge. Other data that were analyzed included demographic factors, severity of illness scores including the Simplified Acute Physiology Score and Acute Physiology and Chronic Health Evaluation (APACHE III) scores, comorbidities, and duration of mechanical ventilation and renal replacement. Patients who died in ICU or were discharged with a plan to limit life support were excluded from this study. For patients who were readmitted to the ICU during the same hospitalization, only the data of their first ICU admission were considered. None of the patients were lost to follow-up or had missing mortality data.

2.1. Statistical analysis

Continuous and discrete data were presented as median with interquartile range (IQR) and count with percentage, respectively. Differences in continuous outcomes with skewed distributions and categorical outcomes were analyzed by Mann-Whitney and χ^2 tests, respectively. Area under the receiver operating characteristic (ROC) curve was used to determine the ability of different predictors in differentiating between patients with and without adverse events after ICU discharge. As some of these biomarkers may not have a linear association with the risk of adverse post-ICU events [16,23], the predictive ability of the biomarkers was further assessed by analyzing them as a categorical variable using the cutoff values previously reported to be useful [12–14,16]. Because of the possibility that dichotomized cutoffs do not accurately capture the usefulness of PCT and CRP, a sensitivity analysis using a restricted cubic spline 3-knot function for PCT and CRP to allow nonlinearity as a continuous predictor in a multivariable model was used to assess whether alternative cut points for these biomarkers were more appropriate [24].

In this study, areas under the ROC curve of >0.70 and >0.80 were considered satisfactory and good, respectively. Multiple logistic regression was used to assess whether each predictor was independently associated with occurrence of adverse outcome after ICU discharge, after adjusting for severity of illness. All analyses were 2-tailed and conducted by SPSS for Windows (version 22.0; IBM, Armonk, NY, 2014) and S-PLUS (version 8.0, 2007; Insightful Corp, Seattle, WA). A P value < .05 was taken as significant in this study.

3. Results

Of the 1877 patients admitted during the study period, 1653 patients (88.1%) were discharged from ICU without treatment limitations (152

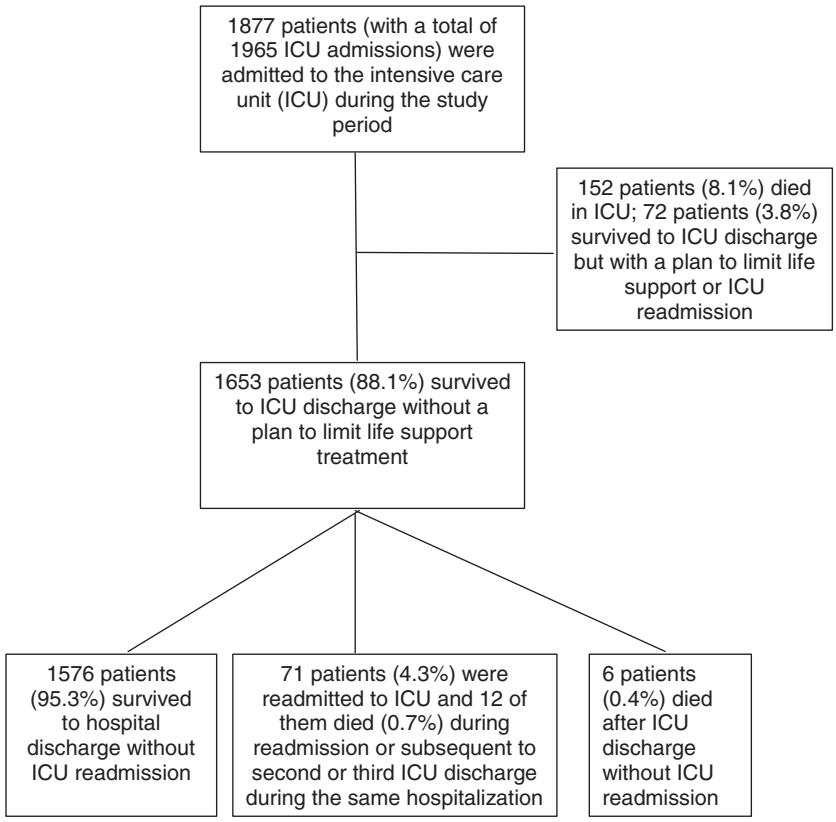

Fig. 1. Flowchart showing inclusion and exclusion of patients for the study.