

CRITICAL CARE



Effect of length of stay in intensive care unit on hospital and long-term mortality of critically ill adult patients

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Background. Critical illness leading to prolonged length of stay (LOS) in an intensive care unit (ICU) is associated with significant mortality and resource utilization. This study assessed the independent effect of ICU LOS on in-hospital and long-term mortality after hospital discharge.

Methods. Clinical and mortality data of 22 298 patients, aged 16 yr and older, admitted to ICU between 1987 and 2002 were included in this linked-data cohort study. Cox's regression with restricted cubic spline function was used to model the effect of LOS on in-hospital and long-term mortality after adjusting for age, gender, acute physiology score (APS), maximum number of organ failures, era of admission, elective admission, Charlson's co-morbidity index, and diagnosis. The variability each predictor explained was calculated by the percentage of the χ^2 statistic contribution to the total χ^2 statistic.

Results. Most hospital deaths occurred within the first few days of ICU admission. Increasing LOS in ICU was not associated with an increased risk of in-hospital mortality after adjusting for other covariates, but was associated with an increased risk of long-term mortality after hospital discharge. The variability on the long-term mortality effect associated with ICU LOS (2.3%) appeared to reach a plateau after the first 10 days in ICU and was not as important as age (35.8%), co-morbidities (18.6%), diagnosis (10.9%), and APS (3.6%).

Conclusions. LOS in ICU was not an independent risk factor for in-hospital mortality, but it had a small effect on long-term mortality after hospital discharge after adjustment for other risk factors.

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Many patients with multiple organ failure require a prolonged stay in an intensive care unit (ICU) before they recover from their critical illness. It has been estimated that between 2% and 11% of critically ill patients require a prolonged stay in ICU,¹⁻⁶ accounting for 25–45% of total ICU days,² ⁷ ⁸ and a significant proportion of resources.⁸⁻¹¹ It has also been reported to be associated with increased mortality and morbidity.^{3 4 6 12 13}

Clinicians have to consider many inter-related factors in making a prognosis regarding outcome in critically ill patients, including age, co-morbidities, severity and irreversibility of the acute illness, physiological reserve, and response to therapy. ¹⁴ ¹⁵ It is possible that prolonged stay

in ICU may be considered a risk factor for poor prognosis by some clinicians because it may represent slow or absent response to ICU therapy.

Previous studies have assessed the effect on mortality of length of stay (LOS) in ICU by categorizing LOS using arbitrary time-points or duration of mechanical ventilation. These were limited by restricted case-mix and insufficient adjustment for predictor variables. The effect of LOS in ICU on long-term mortality after hospital discharge has not been established.

The aim of this cohort study was to examine LOS in ICU as an independent risk factor for in-hospital deaths and long-term mortality after hospital discharge, over and

above the background effect of other risk factors such as age, co-morbidities, severity of illness, gender, and diagnosis. We proposed that LOS in ICU may have a nonlinear, possibly V-shape or bimodal, relationship with in-hospital mortality.

Methods

The study cohort consisted of adult patients who were admitted to the 22-bed general ICU of a tertiary teaching hospital between January 1, 1987 and December 31, 2002. For patients who were admitted to the ICU more than once, only the data of their first ICU admission were included. Patients aged <16 yr, who did not reside in Western Australia (WA) or with incomplete data linkage (3%), were excluded from the study. Although specialist mechanical ventilation weaning units are used in other countries, for example, the USA¹⁶ and the UK,¹⁷ they are not used in WA.

After obtaining approval from the relevant Ethics Committees, the ICU clinical database was linked to two WA administrative databases: (i) the Hospital Morbidity Data System (HMDS) and (ii) the WA Death Register, using probabilistic data linkage. 18 The ICU clinical data were collected prospectively and contained demographic details, ICU admission diagnoses, Acute Physiology and Chronic Health Evaluation (APACHE) II scores¹⁹ and its components, organ failure(s) for each day in ICU and therapeutic interventions. Data integrity was maintained by having a single data custodian during the study period, who checked all data entered and resolved data inconsistencies, and trained the medical staff who collected the data (in total, 14 intensivists) and the clerical staff who entered data (four in total). The HMDS contained data for all public and private hospital admissions in the State since 1980. Each hospital admission was described using up to 21 diagnostic codes and 11 procedural codes, recorded at the time of hospital discharge using the International Classification of Diseases, Ninth Revision, Clinical Modification or Tenth Revision, Australian Modification (ICD-9-CM /10-AM).²⁰ Patients were censored on December 31, 2003 and assumed to be alive if there was no record in the State's Death Register.

Patient characteristics were presented as means and standard deviation (sd), and compared using Student's *t*-tests for normally distributed data and non-parametric tests for non-normally distributed data. In this study, the LOS in ICU was calculated as the number of calendar days from the day of admission (counted as 1 day) to day of discharge (also counted as 1 day unless discharged on the same day as the admission to ICU). The effect of LOS on hospital and long-term mortality (up to 17 yr) was modelled as a continuous predictor by Cox's proportional hazards regression with adjustment for other potential predictors of mortality of critically ill patients. These predictors included age, gender, Charlson's co-morbidity index, acute physiology score (APS) of the APACHE II score,

maximum number of organ failures, era of admission, type of admission (elective surgical, non-elective surgical, and medical), and diagnosis. Diagnoses were grouped into one of nine mutually exclusive categories (cardiac surgery, vascular conditions/surgery, non-traumatic brain condition/surgery, sepsis, trauma, drug overdoses, cardiac arrest, other medical conditions, and other surgery).²¹ The year of the index ICU admission was categorized into four eras, each of a 4-yr period ('1987–1990', '1991–1994', '1995–1998', and '1999–2002').

In the Cox regression analyses, we used a six-knot (up to six angulated changes in the shape of the curve) restricted cubic spline function to allow a non-linear relationship, such as V-shape or multimodal relationship, between LOS and in-hospital and long-term mortality to be modelled to avoid the potential problem of competing effect between short and long ICU stay on mortality. ²² ²³ Restricted cubic spline function is a similar method to using polynomial function and is recommended as a robust way to model the non-linear relationship between LOS and long-term mortality. ²²

During the modelling of long-term mortality, only hospital survivors were included. The relative contribution of each predictor in determining mortality was assessed by the χ^2 statistic minus the degrees of freedom.²² If the χ^2 statistic of a predictor in the model was X and the total χ^2 statistic of the model was Y, the percentage of the predictor in explaining the variability of the outcome would be $100 \times (X-\text{degree})$ of freedom of the predictor)/Y. After the non-linear relationship between the LOS and long-term mortality was modelled, LOS was then categorized according to the break points identified and characteristics of different categories of LOS were compared. Given that most co-variates used in the modelling process are known risk factors for long-term survival as demonstrated in our previous studies, we have included them all as adjustment variables to ensure full adjustment when examining the effect of LOS.²⁴ ²⁵

Data were analysed using SPSS, v16.0 (SPSS; Chicago, IL, USA) and S-Plus (version 8.0 for Windows, 2007; Insightful Corp., Seattle, WA, USA). No interaction terms were included. Two-sided comparisons with 95% confidence intervals (CIs) were used and a *P*-value <0.05 was considered as statistically significant.

Results

A total of 22 298 patients were admitted to the ICU during the study period and 19 921 patients survived to hospital discharge. After adjusting for age, Charlson's co-morbidity index, gender, diagnosis, year of admission, maximum number of organ failures, APS, and elective admission, an increase in LOS was not independently associated with an increased risk of hospital mortality. Most hospital deaths occurred within the first 10 days in ICU.

A biphasic relationship between LOS in ICU and longterm mortality after hospital discharge was observed for both unadjusted (Fig. 1) and adjusted models (Fig. 2). A linear increase in risk of long-term mortality was observed with an increasing LOS until day 10, and after this period, the long-term mortality risk was relatively constant (or close to a plateau) (Fig. 2).

In the 19 921 hospital survivors, the proportion of patients who stayed in ICU for \leq 10 days (94%) was much greater than the proportion of patients who stayed >10 days (6%). The median LOS in ICU for those who stayed >10 days was 17 days (inter-quartile range, 13–24), and these patients accounted for 31% of the total ICU days of the whole cohort. There was an over-representation of trauma and sepsis (P<0.001) in patients who stayed in ICU for >10 days (Table 1). These patients had more severe disease, as measured by the APS and maximum number of organ failures (both P<0.001).

Unadjusted survival was lower for patients who stayed in ICU for >10 days compared with shorter stays (Fig. 3). Although the LOS in ICU was an independent risk factor of long-term mortality, age, Charlson co-morbidity index, diagnosis, and peak numbers of organ failures were all more important risk factors of long-term mortality than LOS in ICU (Fig. 4 and Table 2). The relative contribution of LOS in determining mortality only accounted for about 2.3% of the variability and this was much less than the variability explained by age (35.8%), Charlson co-morbidity index (18.6%), diagnosis (10.9%), and APS (3.6%).

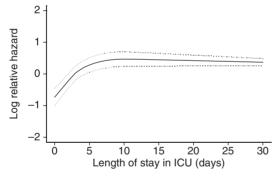


Fig 1 Relationship between long-term survival and length of ICU stay in days without adjusting for other covariates (the dotted lines are 95% CI lines).

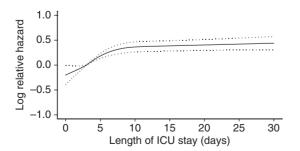


Fig 2 Relationship between length of ICU stay (LOS) and long-term mortality after adjusting for age, sex, diagnostic group, type of admission, peak organ failure, acute physiology score, Charlson's co-morbidity index, and era of admission.

Table 1 Cohort characteristics for the two subgroups of patients who survived to hospital discharge with different LOS: ≤10 and >10 days. *N*, number; sp, standard deviation; IQR, inter-quartile range; KM, Kaplan–Meier; APS, acute physiology score

ICU LOS	≤10 days (N=18 708)	>10 days (N=1213)
Age		
Mean (range)	57 (16-92)	49 (16-86)
Males (%)	68	66
Charlson's co-morbidity index	(
Mean (SD)	0.96 (1.5)	0.77 (1.6)
Median (IQR)	0(0-1)	0(0-1)
APS		
Mean (SD)	6.8 (4.6)	12.4 (6)
Median (IQR)	6 (4-9)	12 (8-16)
Peak number of organ failure		
Mean (SD)	0.76 (0.99)	2.78 (1.41)
Median (IQR)	0 (0-1)	3 (2-4)
Diagnostic group (%)		
Cardiac surgery	50.1	8.9
Vascular disorder/surgery	11.3	4.7
Non-traumatic brain	4.3	6.8
condition		
Sepsis on admission	4.6	23.9
Trauma	7.2	38.6
Cardiac arrest	1.4	1.7
Drug overdose/poisoning	6.0	1.3
Other medical disorder	10.8	11.5
Other surgery	4.3	2.6
Type of admission		
Elective surgical (%)	59.4	10.0
Non-elective surgical (%)	14.9	33.5
Medical (%)	25.7	56.6
Era of admission		
1987-90 (%)	27.9	20.4
1991-4 (%)	29.2	21.1
1995-8 (%)	22.8	28.7
1999-2002 (%)	20.1	29.8
Unadjusted long-term survival	l (KM method)	
One-year survival (%)	94.9	90.8
Five-year survival (%)	83.5	74.9
Ten-year survival (%)	68.2	61.0

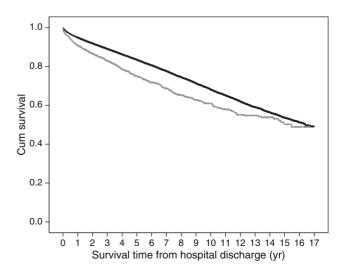


Fig 3 Kaplan Meier survival curve showing long-term survival of patients who survive to hospital discharge (n=19 921) and stay in ICU 10 days or less or longer than 10 days.

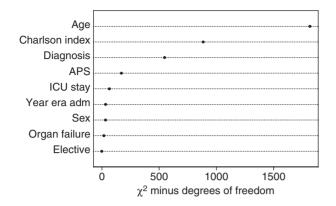


Fig 4 Relative contribution of each predictor in determining the long-term mortality of critically ill patients after hospital discharge. APS, acute physiology score; Charlson index, Charlson's co-morbidity index; elective, elective surgery, non-elective surgery, or medical admission; organ failure, peak organ failure.

Table 2 χ^2 contribution of each covariate in determining the variability of long-term mortality in the Cox proportional hazards model

Covariates	χ^2	df	P-value
Length of stay	67.78	3	< 0.001
Non-linear component	50.44	2	< 0.001
Age	1821.95	5	< 0.001
Non-linear component	9.84	4	0.043
Charlson's co-morbidity index	886.70	2	< 0.001
Non-linear component	65.05	1	< 0.001
Peak organ failure score	18.90	2	< 0.001
Non-linear component	15.56	1	< 0.001
Acute physiology score	174.98	5	< 0.001
Non-linear component	7.97	4	0.093
Elective admission	0.19	2	0.911
Sex	32.02	1	< 0.001
Era of admission	34.92	3	< 0.001
Diagnosis	555.50	8	< 0.001
Total non-linear component	176.19	12	< 0.001
Total	5113.61	31	< 0.001

Discussion

Our results showed that LOS in ICU was not independently associated with an increased risk of hospital mortality. LOS in ICU had a small effect on long-term mortality after hospital discharge, but this long-term mortality effect plateaued after the first 10 days in ICU. Several studies 18-11 have shown that short- and intermediate-term mortality outcomes were worse for patients who had prolonged stays in ICU. One-year survival for patients who had a longer stay was higher in our study compared with the range reported in the literature, 23-81%, $^{26-30}$ but we excluded in-hospital deaths that would have resulted in a lower survival rate if they had been included. In our study, patients who survived 1 yr and who had a prolonged stay had lower unadjusted survival compared with those who had shorter LOS. Four studies have described long-term outcomes among patients admitted to general ICUs with follow-up exceeding 1 yr. Of 157 survivors who stayed in ICU for 14 days and longer, unadjusted 6-, 12-, and 36-month survival was 80%, 75%,

and 67%, respectively.³¹ For 135 patients with either medical conditions or admitted after cardiac surgery and who stayed in ICU for 30 days and longer, 4-yr survival for hospital survivors was 39% in the prolonged stay group compared with 74% in the shorter stay group.⁴ A long-term survival of 64% was found in 68 hospital survivors who stayed in ICU for 28 days or longer and who were followed up for 1–3 yr.³² Five-year survival was 65% in 78 patients who spent >60 days in ICU.²⁹ This survival was lower than the 77% that we found for patients in our ICU whose LOS was >60 days. The small number of studies, differences in case-mix, small samples, lack of adjustment for potential confounders, differences in the definition of 'prolonged' stay and frequent lack of a comparitor group make valid interpretation of the results difficult.

The effect of a prolonged stay in ICU on mortality in critically ill patients remains controversial and uncertain. This is in part due to the different methods of choosing an appropriate break point to define prolonged ICU stay. Reports that described the association of LOS in ICU and mortality chose an arbitrary break point either because it was used in previous publications, represented the 95th percentile of the LOS in the study ICU,^{2 22 33} or when the LOS was 1 sp above the mean.³⁴ No explanation was provided by Gaudino and colleagues³⁵ in their definition of a prolonged stay being >10 days for patients admitted to ICU after cardiac surgery but Bashour and colleagues³⁶ selected ≥10 days because mortality in patients who stay in ICU after cardiac surgery increases rapidly during the first 10 intensive care days.³⁷ One report¹² described the association of LOS and hospital mortality without defining a specific LOS. In this study, in 13 210 patients admitted to a mixed medical-surgical ICU over a 5-yr period, hospital mortality increased with LOS from 1 to 10 days but remained stable, ~35%, for longer LOS.¹² Comparisons between prolonged and shorter stays in this study showed a decreased short-term mortality for the prolonged stay group. It is likely that the wide variations in mortality related to LOS in ICU were due to differences in case-mix and the definition of a 'prolonged' stay in ICU. Our results have improved our understanding of the effects of LOS in ICU on outcomes of critically ill adult patients in several ways. First, the effect of LOS on hospital and long-term mortality was not linear. The LOS had an inverse relationship with the risk of hospital mortality after adjusting for other covariates and a biphasic relationship to long-term mortality. From our regression modelling using robust statistical techniques,²² an apparent cut-off point appeared to occur on day 10 for hospital mortality and long-term survival. This result suggested that most significant short- and long-term effects of the physiological insults of a critical illness occur within the first 10 days of the onset of a critical illness. Secondly, only a relatively small proportion of patients (6%) stayed in ICU for >10 days, and they did so because of the severity of the acute disease. After adjusting for these important risk factors, a prolonged LOS in ICU (e.g. > 10 days) was not independently associated with a higher risk of either hospital or long-term mortality compared with those with LOS ≤ 10 days. Thirdly, although risk of long-term mortality increased with LOS up to 10 days, its effect was small when compared with other risk factors such as age, co-morbidities, diagnosis, and severity of acute illness. Although the costs of caring for patients who require a prolonged stay in ICU is high, their short-and long-term mortality outcome is no worse than those who are discharged from ICU within a shorter time frame. This result suggested that critical care therapy may still be potentially cost-effective for patients who required ICU therapy for a prolonged period. As such, clinicians should be careful not to put undue emphasis on LOS alone in the prognosis of outcomes in critically ill patients.

This study has some significant limitations. First, this was a single-centre study. Although the proportion of our patients who stayed in ICU for >10 days (6%) was very similar to that of other studies, it is possible that other factors specific to this ICU will not be generalizable to other ICUs. Secondly, patients were enrolled over a 16-yr period and there have been changes in the characteristics of patients admitted to ICU and intensive care management. We cannot exclude an effect of changes in therapy on the results of this study. Thirdly, long-term quality of life is important, but we did not have this information on our patients. Finally, although we have adjusted for many confounders of long-term survival, residual confounding by the measured and unmeasured confounders on long-term survival was still possible.

In conclusion, LOS in ICU had a non-linear independent relationship to in-hospital and long-term mortality. The first 10 days of a critical illness was most important in determining in-hospital and long-term mortality, but the independent effect of LOS in ICU long-term mortality was relatively small when compared with age, co-morbidities, diagnosis, and severity of acute illness.

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