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Research paper

# A prolonged intensive care unit stay defines a worse long-term prognosis — Insights from the critically ill mortality by age (Cimba) study

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ABSTRACT

*Background:* Patients with critical illness often survive the intensive care unit (ICU) at a cost of prolonged length of stay (LOS) and slow recovery. This chronic critically ill disease may lead to long-term poor outcomes, especially in older or frail patients.
*Objectives:* The main goal of this study was to address the characteristics and outcomes of patients with prolonged ICU LOS. Mainly, short- and long-term admissions were compared to identify risk factors for persistent critical illness and to characterise the impact on ICU, hospital, and long-term mortality.
*Methods:* Subanalysis of a retrospective, multicentric, observational study addressing the 2-year outcome of patients admitted to Portuguese ICUs (the Cimba study). Patients were segregated according to an ICU LOS of ≥14 days.
*Results:* Data from 37 118 patients were analysed, featuring a median ICU LOS of 4 days (percentile: 25−75 2−9), and a mortality of 16.1% in the ICU, 24.0% in the hospital, and 38.7% after 2 years. A total of 5334 patients (14.4%) had an ICU LOS of ≥14 days (corresponding to 48.9% of all ICU patients/days). Patients with prolonged LOS were more often younger (52.8% vs 46.4%, were ≤65 years of age , $p < 0.001$), although more severe (Simplified Acute Physiology Score II: 49.1 ± 16.9 vs 41.8 ± 19.5, $p < 0.001$), and had higher ICU and hospital mortality (18.3% vs 15.7%, and 31.2 vs 22.8%, respectively). Prolonged ICU LOS was linked to an increased risk of dying during the 2-year follow-up (adjusted Cox proportional hazard: 1.65, $p < 0.001$).
*Conclusion:* Prolonged LOS is associated with a long-term impact on patient prognosis. More careful planning of care should incorporate these data.


## 1. Introduction

Critical care medicine development in the last 50 years has led to a growing capacity for supporting organ failure, lowering mortality of acute illnesses, and allowing survival of patients with low physiological reserve, due to age or previous comorbidities.[1] In addition, advances in medical and surgical treatments, and improved organ support delivery for prolonged periods of time, have allowed patients with very severe illness, old age, and several comorbidities to survive.[2]

This has resulted in a group of patients admitted to the intensive care unit (ICU) who outlast their acute insult but remained dependent on organ-support therapy. These chronic critically ill patients are estimated to be around 5−20%.[3−5] These patients often feature prolonged dependence on organ support, including mechanical ventilation and tracheostomy, and have a prolonged length of stay (LOS) in the ICU.[6] The concept of chronic critical

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illness, although hard to define,[7] is usually considered after 10–14 days of ICU LOS.[8]

Patients with chronic critical illness often have a poor physiological reserve, either acquired during their ICU stay or already previously present and aggravated during the ICU stay. The survival and hospital discharge of these patients often come with the price of impaired functional and cognitive capacity, family burden, and high healthcare costs[9,10] and should be based on the patient's individual features. This is especially hard since chronic critical illness includes a heterogeneous cohort.[5]

Little is still known about the characteristics of this changing population and their long-term outcomes. Most studies addressing this issue evaluated ICU LOS as a continuum and did not focus on the specific population with a long ICU stay. Moreover, knowledge of their long-term prognosis is crucial to empower patients' autonomy and inform medical decisions and health policies, especially regarding therapeutic limitations in the ICU setting.[11] A large database is provided regarding patients with prolonged ICU LOS, addressing their clinical features and long-term outcomes.

## 2. Objectives

The main goal of this study was to address the characteristics and outcomes of patients with prolonged ICU LOS. Mainly, short- and long-term admissions were compared, to identify risk factors for persistent critical illness, and to characterise the impact on ICU, hospital, and long-term mortality.

## 3. Methods

This is a subanalysis of the critically ill mortality by age (Cimba) study. The study protocol has been published elsewhere.[12] Briefly, all adult patients admitted for more than 24 h during a 4-year study period (January 2015 to June 2019) from 16 different Portuguese hospitals were included between June and December 2020. Information collected included age, gender, the main reason for admission (medical, elective, or urgent surgery), Simplified Acute Physiology Score (SAPS II), and evidence of sepsis (diagnosed by local criteria). Patients were followed until discharged from the hospital (dead or alive) and until 2 years of follow-up. After data retrieval, there was anonymisation and collection into a central database.

The study protocol was approved by the Hospital Vila Franca de Xira Ethics Committee (decision number 29/20) on 01-10-2020. Informed consent was considered unnecessary due to the study's retrospective and anonymous nature. The study was approved by the local research and ethics committees of all participating centres.

In this subanalysis, the cohort was split into two groups according to their ICU LOS: short (<14 days) and prolonged (≥14 days). Risk factors for prolonged ICU were identified. The ICU and hospital mortality were compared between the two groups.

General descriptive statistics were used. Continuous variables were reported as mean ± standard deviation, or median [percentile 25 – percentile 75], according to data distribution. Categorical variables were reported in N and percentage. Clinical and continuous baseline demographic data were compared with the Student T test or Mann–Whitney U test, according to data distribution. For categorical data, the Chi-square test was used. A multiple regression model was used to identify risk factors for a prolonged ICU LOS. To evaluate the long-term mortality, the Kaplan–Meyer survival curves (from day 14 to 2 years of follow-up) were plotted for the whole population (split according to the ICU LOS) and for the subgroups of patients divided by age (<65 years or ≥65 years). The Cox proportional hazard was used to compare long-term mortality risk between groups. Age and SAPS II–adjusted hazards ratios were computed with the 95% confidence interval (CI). All statistics were two-tailed, and the significance level was defined as $p < 0.05$. Statistical analysis was performed using STATA 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

## 4. Results

Data were collected from 16 different centres in Portugal, which included about 65% of all available beds from Portuguese ICUs at the time of the study.[12] The original sample included 37 118 patients (Fig. 1): 60.1% were male, and 52.7% were older than 65 years (Table 1). The median ICU LOS was 4 days.[2–9] All patients completed at least 1 year of follow-up. A second year was available for 80.8% ($n$ = 19 201) of the survivors (the remainder 19.2% included in the dataset were admitted to the ICU less than 2 years before the study conclusion, and due to study design, it was not possible to follow them anymore as data were already being analysed). Most patients were admitted due to medical conditions (63%); the remaining ones were admitted due to urgent and elective surgical procedures (25.2% and 11.8%, respectively). The mean SAPS II was 42.8 ± 19.4, and sepsis was diagnosed in 31.3% (missing information for 493 patients). The overall ICU mortality was 16.1% ($n$ = 5982); hospital mortality was 24%, and cumulative long-term mortality was 31.7% after 1 year and 41.0% after 2 years of follow-up.

From all cohorts, 5334 (14.4%) patients had an ICU LOS of ≥14 days. Their demographic and clinical characteristics are presented in Table 1. Their median LOS was 21 [16.5–28.6] days, which corresponded to 48.9% of the whole population patient/days. Accordingly, these patients also had significantly more expensive hospital stay, and an estimated mean cost of €45,472.9 ± 26,889 per patient, compared to a mean of €12,627 ± 9701 per patient with an ICU LOS of <14 days; their estimated cost per day was actually lower (estimated at €1452/day for the long-stay patients and €1715/day for the short-stay patients) since individual daily costs tend to decrease during the ICU stay.[13,14] Both the ICU and hospital mortality were higher in the group with prolonged ICU LOS (Table 1; Supplementary Fig. 1). Interestingly, this mortality risk difference was significantly more evident in older patients (Fig. 2, Panel A2 and B2, and Supplementary Fig. 1).

In the multiple regression model, an age of ≤65 years (odds ratio: 1.67, 95% CI: 1.57–1.77), a diagnosis of sepsis (odds ratio: 1.35, 95% CI: 1.26–1.43), and SAPS II (per point odds ratio: 1.02; 95% CI: 1.02–1.02) were identified as independent risk factors for prolonged ICU stay (Supplementary Table 2).

The Kaplan–Meyer survival curves were plotted according to ICU LOS (<14 days vs. ≥14 days) for the whole population and the subgroups, divided by age (Fig. 2). Only patients who survived for at least 14 days were included (to prevent a survivor bias). Overall, 30 892 patients were evaluated (Supplementary Table 1). The adjusted hazards ratio for 2-year mortality for prolonged ICU LOS was 1.65 (95% CI: 1.58–1.73, $p$ < 0.001) (Table 2).

## 5. Discussion

### 5.1. *Key findings*

In this study, it was found that 14% of patients admitted to an ICU during a 4-year period had a prolonged LOS, which corresponds to almost 50% of all ICU patient/days. Independent risk factors for this prolonged ICU stay were an age of <65 years, the presence of sepsis, and a higher SAPS II. Not surprisingly, in the present study, patients with prolonged ICU stay had higher ICU and hospital

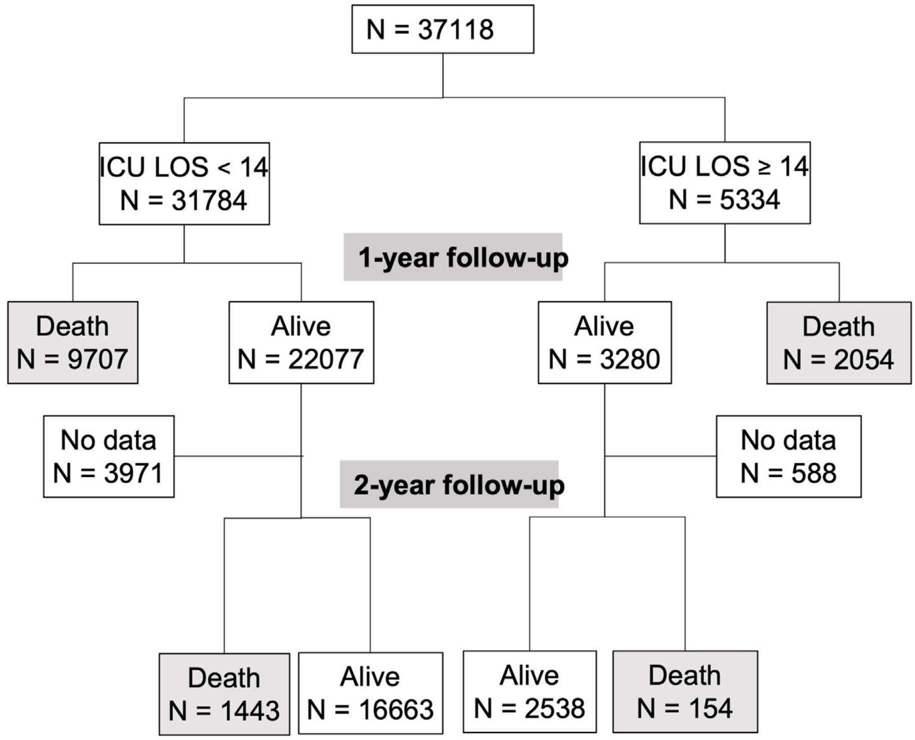


**Fig. 1.** Patient inclusion according to length of stay. ICU LOS – intensive care unit lngth of stay.

**Table 1**
Demographic characteristics and mortality of patients of all cohorts, divided according to the intensive care unit length of stay.

| | Total | LOS < 14 | LOS ≥ 14 | *p* |
|---|---|---|---|---|
| N | 37118 | 31784 (85.6) | 5334 (14.4) | |
| ICU length of stay, median (IQR) | 4 (2–9) | 3.6 (2–6.1) | 21 (16.5–28.6) | <0.001 |
| Age above 65 years, *n* (%) | 19553 (52.7) | 17034 (53.6) | 2519 (47.2) | <0.001 |
| Male gender | 22294 (60.1) | 18790 (59.1) | 3504 (65.7) | <0.001 |
| SAPS II | 42.8 ± 19.4 | 41.8 ± 19.5 | 49.1 ± 16.9 | <0.001 |
| Sepsis, *n* (%)[a] | 11448 (31.3) | 9398 (29.9) | 2050 (39.3) | <0.001 |
| Reason for admission | | | | |
| Medical | 23370 (63.0) | 19983 (62.9) | 3387 (63.5) | 0.39 |
| Surgical urgent | 9359 (25.2) | 7598 (23.9) | 1761 (33.0) | <0.001 |
| Surgical elective | 4389 (11.8) | 4203 (13.2) | 186 (3.5) | <0.001 |
| ICU mortality | 5982 (16.1) | 5004 (15.7) | 978 (18.3) | <0.001 |
| Hospital mortality | 8916 (24.0) | 7250 (22.8) | 1666 (31.2) | <0.001 |
| 1 year mortality | 13143 (35.4) | 10907 (34.3) | 2236 (41.9) | <0.001 |
| 2 year mortality[b] | 13358 (38.7) | 11150 (40.1) | 2208 (46.5) | <0.001 |

Demographic and mortality of patients according to the intensive care unit length of stay. ICU – intensive care unit; LOS – length of stay; IQR – 25–75% interquartile range; SAPS – Simplified Acute Physiology Score.
[a] Missing data for 493.
[b] $n = 32559$, with 2-year follow-up complete.

mortality. Notwithstanding, this was also associated with a high risk of 2-year mortality, particularly striking in older patients.

### *5.2. Relationship with previous literature*

The study population was divided by an ICU LOS of ≥14 days, according to the definition of chronic critically ill disease used in several different studies,[15,16] to include a more homogenous group of persistently sick patients. Accordingly, the association between this prolonged ICU LOS and short- and long-term outcomes was able to be evaluated.

The prevalence of prolonged ICU LOS in the present study concurs with recent chronic critically ill studies, which reported a prevalence between 8% and 20%.[17,18] The reported variability might be linked to the case mix of patients admitted, with a higher incidence in the medical or trauma populations[19] or to different cultural beliefs promoting prolonged organ-support time. The present data suggest a higher prevalence of prolonged ICU LOS in nonelective surgical patients. These might be related to an elevated incidence of trauma in the current study cohort. Trauma patients frequently require prolonged ICU stay due to neurological injury, persistent organ dysfunction, and rehabilitation needs.[20,21] This might also explain why younger patients more frequently had a prolonged ICU LOS in the present cohort. Nevertheless, the present study did not include data collection on this specific issue. In addition, elderly patients often die or are discharged in the first days of ICU LOS, and seldom stay for longer periods. This is probably related to their higher incidence of comorbidities, and an overall

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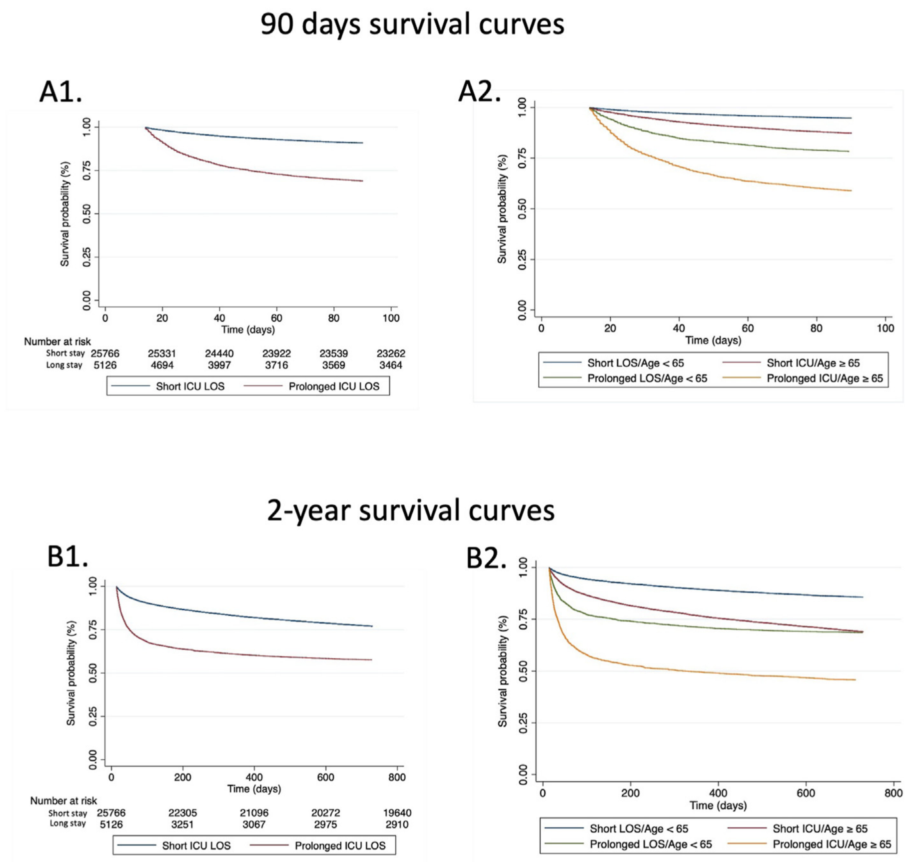


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| Time | Plot | Category | Log Rank | LogRAnK p value |
|---|---|---|---|---|
| 90 days | Plot A1 | < 14 vs ≥ 14 | 75.4 | < 0.001 |
| | Plot A2 | < 14 vs ≥ 14/ ≤ 65 vs > 65 | 79.1 | < 0.001 |
| 730 days | Plot B1 | < 14 vs ≥ 14 | 882.8 | < 0.001 |
| | Plot B2 | < 14 vs ≥ 14/ ≤ 65 vs > 65 | 905.3 | < 0.001 |

**Fig. 2.** Kaplan–Meyer Survival curves of patients according to the intensive care unit length of stay (>14 days) and age (>65 years). Below is the table with the Cox proportional rank test results for each curve.

**Table 2**
Adjusted Cox proportional hazard ratios for 2-year mortality.

| | Hazard ratio | 95% CI | *p* |
|---|---|---|---|
| ICU LOS >14 days | 1.65 | 1.58–1.73 | <0.001 |
| Age >65 years | 1.96 | 1.88–2.04 | <0.001 |
| SAPS II | 1.02 | 1.01–1.02 | <0.001 |
| Sepsis | 1.02 | 1.01–1.02 | 0.12 |

CI – confidence interval; ICU LOS – intensive care unit length of stay; SAPS – Simplified Acute Physiology Score.

higher burden of critical illness, which foster doctors to an early limitation of their therapeutic efforts.[22,23] Frailty is also a significant problem in the elderly population and can reach more than one in five admitted patients.[24] Furthermore, ICU stay may also contribute to aggravating frailty itself.[25]

Of note, sepsis was also associated with a higher incidence of prolonged ICU LOS, as reported in another very large cohort.[26] The early identification of high-risk patients for prolonged ICU LOS can lead to personalised interventions to decrease nosocomial infection, immune and cognitive dysfunction, and other morbidities.[27] On the other hand, knowledge of short- and long-term prognoses may facilitate patients' and family's autonomy and goals-of-care decisions.[24]

The impact of a prolonged ICU LOS on the outcome has been heterogeneously reported. In the present study, a prolonged ICU LOS was associated with a worse outcome in the ICU and in the hospital, contrary to what was reported in a cohort of critically ill patients with cancer.[28] This has also been suggested by a 2007 study, which included a heterogeneous population: a 33% mortality for patients with ≥10 days of LOS compared with 15% for those with 5 days of LOS.[29] Interestingly, in that study, mortality increased with ICU LOS up until the 10th day, remaining stable afterwards.

However, after ICU discharge, the long-term outcome remains influenced by the ICU LOS. In the present study, this increase in mortality risk was independent of severity on admission and persisted for at least 2 years, being more remarkable in the older population. This was also reported in a French study, including patients admitted between 2013 and 2016.[30] This long-term risk has been largely described for sepsis, namely increased mortality[31] or significant morbidity.[30,32] According to the present-study findings, this may well apply to all the intensive care population. Curiously, Szakmany et al. reported that patients discharged home directly from the ICU had a better prognosis,[33] suggesting that the ICU environment might also provide more efficient rehabilitation plans, albeit with higher costs.

Physicians may often rely most on ICU survivorship as the main outcome of interest. However, a prolonged ICU stay, with increased disability and short-term survival after Hospital discharge, may not be in the patient's best interest.

Most studies address ICU LOS as a continuous variable.[34] However, this limits the study of the specific population with prolonged ICU LOS, which, in the present study cohort, corresponded to almost 50% of all ICU patient/days. Others have used a similar methodology but with different cut-off points (8[35] or 10 days[5]). A cut-off of 14 days was chosen as this is the most consensual definition of chronic critical illness. Due to the high variability of the selected cut-off, there are limited data addressing these populations.

The use of machine learning to achieve better prognoses for these populations has also been proposed. However, the ethical issues regarding such an approach must also be considered,[36] especially considering that quality of life is hard to define and largely subjective and that using standard definitions may be associated with a risk of injustice against individuals or groups of patients.[36]

## 6. Strengths and limitations

This study has several limitations: First, due to pragmatic reasons, a very limited number of comorbidities were collected. This may have introduced bias in the evaluation. For instance, data were not collected on trauma, several comorbidities, or frailty. In addition, this was a retrospective analysis, and there were no available data regarding functional outcomes, and no conclusion can be drawn on the quality of life after discharge. It was a single-country study, no data on religious or social-cultural beliefs were collected, and these could have influenced the current results. A complete 2-year follow-up was not achieved for roughly 20% of the 1-year survivors. Although this population results from temporal criteria only, it might have introduced some unpredictable bias for the 2-year follow-up conclusions.

It also has some strengths: it is based on a large database, is multicentric, and involves more than half of all ICU patients admitted for more than 24 h in a Portuguese ICU, during a 4-year period.

## 7. Conclusions

Patients with a prolonged ICU LOS have an increased risk of dying in the hospital and during the first 2 years of follow-up. This risk is likely to be higher in the older population.

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## CRediT authorship contribution statement

JGP, AO designed the study; ARR, SMF, AO, TV acquired the data; ARR and SMF and performed a literature search; ARR, SMF analysed and interpreted the data; SMF and JGP provided the statistical expertise; JGP, AO; TV, ARR, SMF revised the manuscript for important intellectual content; All authors review and approved the final manuscript. JGP acts as the guarantor of the integrity and accuracy of the data.

## Conflict of interest

Not applicable.

## Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aucc.2024.03.001.

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