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Factors associated with mortality in severe community-acquired pneumonia: A multicenter cohort study

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Objective: Describe characteristics and outcomes of CAP admitted to public ICUs in Brazil.
Methods: Retrospective cohort study in 4 Tertiary Public Hospitals in Rio de Janeiro, Brazil *during 2016.* Patients admitted to ICUs with a diagnosis of community-acquired pneumonia were included. Clinical and outcomes data were collected from Epimed Monitor System.
Results: From 7902 admissions, 802 patients (10, 1%) were included and analyzed. Main source of admission was the emergency department (78, 3%). Median age was 66 (IQR 54–77) years, SAPS3 71(IQR 58–83) and SOFA D1 9 (IQR 5–12) points. 67% of patients needed invasive mechanical ventilation, 12% hemodialysis. 47% required vasopressors. ICU and hospital mortality were 55.9% and 66.5% respectively. In a multivariate analysis, malnutrition [OR 2.28(1.21–4.3)], septic shock at admission [OR 1.95(1.39–2.75)], AIDS [3.04(1.16–7.93]), invasive mechanical ventilation [5.07(5.54–7.27)], age > 65 years [2.07(1.48–2.90)] and LOS >1 day before ICU admission [1.90 (1.34–2.71)] were associated with increased mortality.
Conclusion: CAP is associated with high mortality in patients admitted to public ICUs in Brazil. The current findings may help improve resource allocation and should aim at improving access to ICU care since delayed admission was associated with increased hospital mortality.

1. Introduction

Community acquired pneumonia (CAP) is a frequent and life-threatening cause of admission to intensive care units (ICU) [1,2,3]. With increases in life expectancy and better clinical management of severe chronic diseases the rates of hospital and ICUs admissions due to CAP are growing [4] challenging the healthcare systems, especially those with limited resources. In Brazil, CAP is the number one cause of ICU admissions [5] and to hospitals according to data from the Unified Public Health System (SUS) accounting for 700,000 cases per year [6]. Recent studies demonstrate improvements in sepsis mortality worldwide [7], however in Brazil sepsis in the ICU is still associated with exceedingly high mortality rates up to 55% in public hospitals [8]. Despite the growing literature on sepsis' characteristics and outcomes in low-middle income countries [8,9,10], most data from ICUs includes all sepsis patients regardless OF its source of acquisition, thus mixing community-acquired and nosocomial infections [11]. A better understanding of clinical picture, outcomes and potentially modifiable risk factors associated with mortality are key to improve the management of this condition and implement strategies that can improve survival of patients with severe CAP.

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The aim of the present study was to describe the clinical characteristics, outcomes and factors associated with increased mortality in a contemporary cohort of patients with severe CAP admitted to ICUs in public hospitals in a middle-income country.

2. Patients and methods

This is a retrospective analysis of a cohort with prospectively collected data from patients admitted to 16 general ICUs (171 beds) in 4 tertiary public hospitals in the metropolitan area of Rio de Janeiro, Brazil. Patients were included *between January 1st 2016 and December 31st 2016.*

All ICUs work in a closed model, with a board-certified intensivist in charge of the management and of the daily multidisciplinary rounds. The access to all beds is anaged by the State Regulation Centers' (CER) network with the aim to organize and prioritize the admission to intensive care units. Regulation of ICU beds is based on technical priority criteria, following hierarchical protocols built on consensus by medical specialty societies, giving priority to cases of higher severity [12,13].

In order to calculate the sample size, it was estimated a 60% mortality rate (based on data from public hospitals in the Spread study [8] and in the Epimed Monitor Database [5], with an absolute precision of 5% and a significance level of 5%, and it was necessary to include 369 patients. However, the study included the total population available at the time that allowed us not only to be above the minimum sample size to ascertain the power of the study but also to be able to explore more information and subgroup analysis.

This study was strictly observational and did not interfere with clinical decisions related with patient care. The study was approved by The Ethics Committee of Instituto D'OR: CAAE 64831717.0.0000.5249 and the need for informed consent was waived.

During the study period, every patient admitted in the adult ICUs with a diagnosis of community-acquired pneumonia was included. We retrieved de-identified patient data from the Epimed Monitor System (www.epimedsolutions.com, Epimed Solutions, Rio de Janeiro, Brazil), a cloud-based registry for ICU quality improvement and benchmarking purposes, described elsewhere [5].

In brief, patient data are routinely registered in the system, including demographics, the Simplified Acute Physiology Score (SAPS) 3, the Sequential Organ Failure Assessment (SOFA), comorbidities based on the Charlson comorbidity index, functional capacity as described by the Eastern Cooperative Oncology Group (ECOG) performance status (PS) in the week before hospital admission, ICU admission diagnosis, life-sustaining therapies, ICU and hospital length of stay (LOS) in days, vital status at ICU and hospital discharge. Delay in ICU admission was defined as the time from hospital admission to ICU admission in days. Septic shock was defined using the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [14]. Exclusion criteria for the data analysis were missing core outcomes, disease severity data or ICU readmission status.

The primary outcome of interest was all-cause hospital mortality.

2.1. Data presentation and statistical analysis

Standard descriptive statistics were used. Continuous variables were reported as median interquartile range (IQR). Data for LOS were available in days, and we assumed that each day represented a 24 h period even at the beginning and the end of the LOS. Univariate analysis was used to identify factors associated with hospital mortality. Univariate and multivariate logistic regression were used to identify factors associated with hospital mortality. Variables yielding *P*-values below 0.2 by univariate analysis were entered into a forward multivariate logistic regression analysis, clinically plausible variables were forced in the model regardless of its original P-value. Multivariate analysis results were summarized by estimating odds ratios (OR) and respective 95% confidence intervals (CI). Two-tailed P-values <.05 were considered statistically significant. The PASW Statistics 18.0 software package (Chicago, Illinois, USA) was used for statistical analysis.

3. Results

3.1. Patient population

During the study period, 7902 patients older than 15 years were admitted and 902 (11,4%) patients had a clinical diagnosis of severe CAP. After exclusion criteria were applied 802 patients were analyzed (Fig. 1). We excluded patients with lack of core outcome data (ICU and hospital). However, when we performed a comparison, the groups had similar severity of illness as evaluated by SAPS 3 and organ failure scores (Supplement table I).

As expected, most patients were admitted directly from the emergency department (ED) ($n = 630$, 78.5%), and the remaining were transferred from another healthcare unit ($n = 128$,16%) or admitted from the wards and another ICU in the same hospital ($n = 23$, 2,8% and $n = 21$, 2.6% admissions, respectively),all of them with initial diagnosis of CAP. The patient's main characteristics are shown in Table 1. The median age was 66 (IQR 54–77) years and 42.8% were women. Five hundred and thirty five patients (67%) required invasive mechanical ventilation and 96 (12%) used renal replacement therapy. As demonstrated by the median SAPS 3, SOFA scores and Charlson index patients were severely ill, with multi-organ failure and presented a high-burden of co-morbidities (Table 2). Three hundred and seventy six patients (47%) had septic shock on ICU admission. The most frequent comorbidities were *diabetes mellitus (26.4%),* cardiac failure (20.6%), *Chronic Obstructive Pulmonary Disease (20.6%),* chronic renal disease (14.6%), *malnutrition (10.6%), alcoholism (8.4%), dementia (6.4%), AIDS (4.9%) and* Cancer (4.7%). Poor functional capacity before hospital admission (PS 3 and PS 4) was identified in 10.6% of the patients.

3.2. Main outcomes

The ICU mortality was 56% and the hospital mortality was 66,5%. Tables 1 and 2 show the factors associated with hospital mortality in the univariate analysis of the entire cohort. As expected, age, disease severity (SAPS 3 and SOFA), Charlson index, renal replacement therapy, mechanical ventilation, time in hospital before ICU admission, hospital and mechanical ventilation length of days, septic shock on admission, poor perfomance status before ICU admission (PS 3 and PS 4),

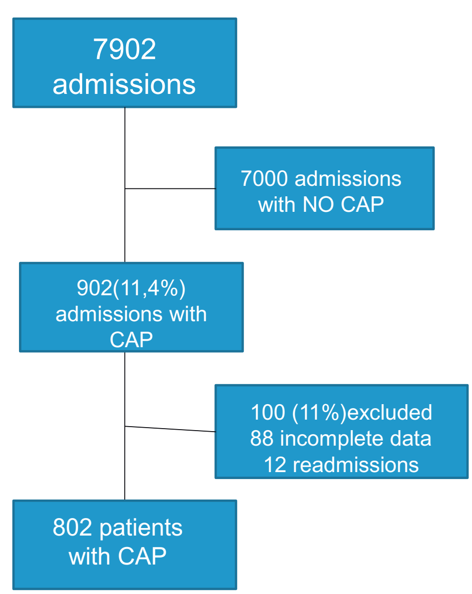

Fig. 1. Study Flow chart CAP: Community-acquired Pneumonia.

Table 1
Patients' characteristics and comparison according to hospital survival.

	All Patients		Non-survivors		Survivors		p-value
	n = 802		n = 533		n = 269		
	100%		66.5%		33.5%		
	n	%	n	%	n	%	
Median age (years)[a]	66 (54–77)	- -	69 (58–79)	- -	63 (44–72)	- -	<0.001
Male gender	416	51.9%	279	67%	137	33%	0.765
SAPS 3[a]	71 (58–83)	- -	76 (67–87)	- -	57 (50–68)	- -	<0.001
SOFA D1[a]	9 (5–12)	- -	11 (7–13)	- -	5 (2–9)	- -	<0.001
Charlson[a]	2 (0–3)	- -	2 (0–3)	- -	1 (0–3)	- -	0.025
LOS before ICU median[a]	1 (0–2)	- -	1 (0–2)	- -	1 (0–1)	- -	0.002
PS 3 and 4	85	10.6%	68	0,8	17	20.0%	<0.005
Septic shock on admission	376	46.9%	295	79%	81	21.5%	<0.001
Dementia	51	6.4%	41	80.4%	10	19.6%	0.032
Alcoholism	67	8.4%	44	65.7%	23	34.3%	0.892
Malnutrition	85	10.6%	71	66.5%	14	16.5%	<0.001
Diabetes Mellitus	212	26.4%	149	70.3%	63	29.7%	0.176
AIDS	39	4.9%	33	84.6%	6	15.4%	0.014
COPD	165	20.6%	104	63.0%	61	37.0%	0.309
Chronic renal disease	117	14.6%	77	65.8%	40	0,342	0.916
Cardiac Failure	165	20.6%	101	61.2%	64	38.8%	0.115
Cancer	38	4.7%	29	76.3%	9	23.7%	0.220

Definition of abbreviations: IQR interquartile range 25%–75%, PS = performance status; COPD = chronic obstructive pulmonary disease; SOFA D1 = sequential organ failure assessment score on admission day; SAPS 3 = simplified acute physiology score.
[a] Data are n (%) or median (IQR).

malnutrition, dementia and AIDS were associated with hospital mortality. The standardized mortality ratio (SMR) was 1.21 according to SAPS 3 standard equation.

In a multivariate logistic regression, variables independently associated with in-hospital mortality were: mechanical ventilation, AIDS, malnutrition, age > 65 years, septic shock on admission and delay in ICU admission >1 day (Table 3 and Fig. 2). We created a second multivariate model with the variable transfer from another ICU (Supplement table II) and the model was stable showing also the impact of transfer in mortality. Other variables were similar to those in the first model.

To evaluate the access to intensive care we performed a comparison between patients admitted to ICU with <1 day of hospital admission (n = 355) and those with >1 day (n = 447). The main differences were a more frequent need of mechanical ventilation and a higher rate of patients with a poor functional capacity (performance status groups 3 and 4) in the group admitted to ICU with <1 day of hospital admission (Table 4). According to SAPS 3 standard equation, SMR was 1,14 in the group admitted to ICU with <24 h and 1.25 in the later group.

Table 2
Patient's outcomes and comparison according to hospital survival.

	All patients		Non-survivors		Survivors		p-value
	n = 802		n = 533		n = 269		
	100%		66.5%		33.5%		
	n	%	n	%	n	%	
MV LOS[a]	8(3–18)	- -	6(3–13)	- -	8(3–13)	- -	0.042
ICU LOS[a]	6(3–13)	- -	7(3–14)	- -	11(6–23)	- -	0.700
Hospital days[a]	11(5–19)	- -	9(5–17)	- -	14(8–25)	- -	<0001
RRT	96	12.0%	73	76.0%	23	24.0%	0.038
MV	535	67.0%	420	0,785	115	21.5%	<0.001

Definition of abbreviations: IQR interquartile range 25%–75%, LOS = length of stay in days; ICU = intensive care unit; RRT = renal replacement therapy; MV = mechanical ventilation.
[a] Data are n (%) or median (IQR).

Table 3
Multivariate analysis of predictors of hospital mortality in all patients admitted to the ICU with CAP (n = 802).

Variables	OR (95% CI)	p value
Mechanical Ventilation	5.07 (3.54–7.27)	<0.001
AIDS	3.04 (1.16–7.93)	0.023
Malnutrition	2.28 (1.21–4.30)	0.011
Age > 65 years	2.07 (1.48–2.90)	<0.001
Septic shock on admission	1.95 (1.39–2.75)	<0.001
Delay in ICU admission > 1 day	1.90 (1.34–2.71)	<0.001

Hosmer-Lemeshow goodness-of-fit (X^2 = 8.689; P = .369).

4. Discussion

The present study demonstrates exceedingly high hospital mortality for critically ill patients with severe CAP in tertiary public hospitals in a middle-income country. We showed that pre-existing factors as severe comorbidities, age, severe presentation of acute illness septic shock, mechanical ventilation were independently associated to hospital mortality. Interestingly, an organizational (days in hospital before ICU) factor had significant impact on the odds of hospital survival. The acknowledgement of this potentially modifiable aspect should be a target for interventions that change the improve triage and reduces the delays in access to intensive care.

Previous studies already demonstrated elevated mortality rates in CAP patients admitted to ICUs, mainly in limited resourced health systems, including Latin American countries [15,16,17,18]. Our results confirm the previous findings and also show higher than expected risk-adjusted mortality rates as observed by the standardized mortality ratios (SMR = 1, 21).

There are many potential explanations for the present results. Since 2008 the National Emergency Care Policy implemented Emergency Care Units (UPA) as facilities of intermediate complexity between primary care and the hospital system in Rio de Janeiro [19,20]. Despite the improved access of less sick patients to healthcare with a potential benefit in decreasing the use of emergency rooms, a delay to ICU admission was still observed because of hospital bed shortage, mainly in the ICUs [13]. In the present study, we compared patients regarding the status of earlier (<1 day) versus delayed (>1 day) admission to intensive care and we observed that despite the elevated rate of life-sustaining therapies in both groups, there was a higher rate of mechanical ventilation in the group of patients admitted earlier. It is only natural that respiratory failure as a life-threatening condition would be a driver of earlier referral to an ICU bed. However, surprisingly the early admission group also had a higher frequency of patients with poorer performance status (PS). This apparently paradoxical finding, a triage showing preferential access of sicker patients but neglecting aspects of previous morbid conditions and functional capacity, reflects a system based on severity and the lack of inclusion of functional capacity, co-morbidities and other premorbid conditions in the assessment. When we plotted some usual scenarios (Fig. 2) and observed that, as expected, we could see incremental mortality as we added risk factors. This simple observation may be of use to illustrate the actual mortality rates associated with easily recognizable clinical pictures.

Recent data shows that integrating a systematic triage model containing valid criteria to ICU admission to the usual practice can improve the process [29]. In our population, the present observation probably reflects use of MV as the surrogate of severity in a system that is overwhelmed by demand for ICU beds, but also to the fact that data on functional capacity and co-morbities is not usually captured and made available when critically ill patients are evaluated. A recent study with almost 60,000 patients admitted to Brazilian ICUs demonstrate that functional capacity as measured by the performance status is an independent predictor of hospital mortality and can increase the predictive ability of ICU scoring systems [21].

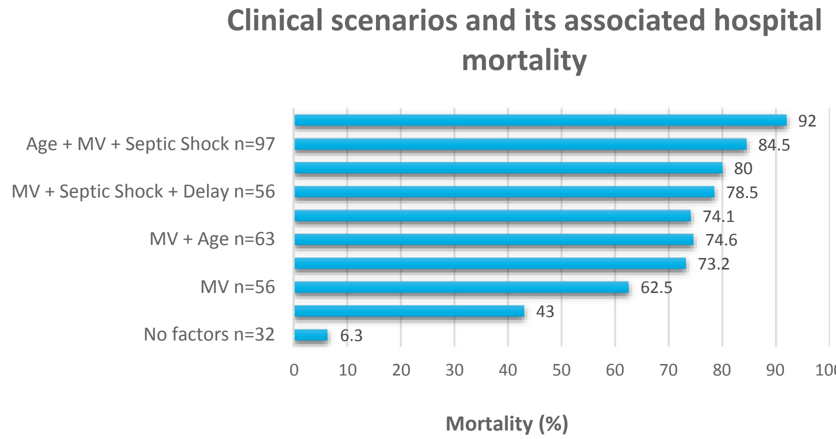

Fig. 2. Definition of abbreviations : MV=Mechanical Ventilation, Age=patients older than 65 years, Delay=delay in ICU admission longer than 1 day.

In line with our findings, other authors also observed the excess of mortality in patients who had delayed ICU admission [22,23]. Cardoso et al. showed mortality as high as 57% in ICU admissions longer than 24 h in a Brazilian Teaching Hospital [24]. Because of the busy nature of a ED practice, which entails simultaneous responsibilities for numerous patients of varying severities of illness, physicians and nurses may not be able to provide the focused care in a timely way that a critically ill patient requires. It is also possible that there may be a different level of critical care expertise among the physicians and nurses who care for the patients who await ICU transfer, compared with the critical care expertise of the staff in the ICU, this would potentially delay the interventions that are associated with improved outcomes when implemented in a time-sensitive fashion [26,30].

The challenges to improve the care of septic patients in Brazil have been highlighted in recent years [8,9] and efforts have been carried out with heterogenous results, that are however worse in public hospitals [25,26]. Despite the increase in the total number of ICU beds from the Public Health System in recent years [27] it remains unequally distributed and the access to these beds is still a complex piece of this puzzle [31].

Table 4
Patients admitted less and >1 day of hospital admission: Main characteristics and univariate analysis.

	<1 day admission (n = 355)	>1 day admission (n = 447)	*P* value
Age (years)	67 (54–77)	66 (54–78)	0.794
Male gender	195 (47.0%)	221 (53.0%)	0.135
SAPS 3	71(59–82)	71(57–83)	0.772
SOFA Day 1	9 (5–13)	8 (5–12)	0.105
Charlson index	2(0–3)	2(0–3)	0.806
MV	274 (77.0%)	261(58.3%)	<0.001
Septic Shock on admission	170 (47.9%)	206 (54.8%)	0.619
RRT	40 (11.3%)	56 (12.6%)	0.662
PS 3/4	48 (13.5%)	37 (8.3%)	0.021
Cardiac failure	66 (18.6%)	99 (22.1%)	0.22
Chronic renal disease	45 (12.7%)	72 (16.1%)	0.191
Cancer	17 (4.8%)	21 (4.7%)	1.00
COPD	72 (20.3%)	93 (20.8%)	0.861
AIDS	12 (3.4%)	27 (6.0%)	0.098
Diabetes Mellitus	97 (27.3%)	115 (25.3%)	0.629
Dementia	21 (5.9%)	30 (6.7%)	0.665
Alcoholism	27 (7.6%)	40 (8.9%)	0.523
Malnutrition	30 (8.5%)	55 (12.3%)	0.084

Definition of abbreviations: PS = performance status; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; SOFA score = sequential organ failure assessment score; SAPS score = simplified acute physiology score; RRT = renal replacement therapy; MV = mechanical ventilation.

Our study has some strengths. First, we analyzed a large number of consecutive patients admitted to public hospitals, and the public sector represents the setting where roughly 75% of Brazilians are exclusively treated [28]. Second, as we studied exclusively patients with CAP diagnosis at admission, it can provide a more homogeneous population as compared to sepsis studies and factors that are associated to mortality, as well as the potential solutions to the identified problems are probably very different when community and hospital acquired sepsis is compared. Also, we collected robust baseline clinical characterization including pre-admission data on functional capacity. Finally, we could demonstrate the delay in access to critical care as an important factor associated with poorer outcomes as observed in higher SMR in the later admissions to ICU group.

There are also several limitations to our study. First of all, we didn't have access to the exact time that elapsed from the initial emergency unit assessment (primary care) to hospital and from ED in the hospital to ICU. Additionally, due to the focus on ICU patients, data on patients that died before ICU admission was not available even of patients hospitalized in another unit other than the ED (wards and another ICU). We acknowledge they could represent a sicker population or those that represented more indication of end of life care or simply those that failed to receive adequate resuscitation in due time. Therefore, the actual mortality of severe CAP patients presenting to the hospitals in need of ICU care may be even higher. Another limitation of our study was the lack of data from patients with delayed admission to ICU that could helps us to develop a propensity score to better understand factors related to this delay. Additionally the process of care was not measured, such as: adherence to surviving sepsis campaign bundles, antimicrobial guidelines, ventilatory support care, among others. But recent studies shows that the overall adherence is low and that the implementation of such measures can help to partially improve outcomes in Brazilian public hospitals, a factor that could also represent that currently recommended measures are not applicable or have little potential on the reversibility of those presenting late and with established organ failures [32]. Finally, no microbiological data was provided during the study so we do not know if a high incidence of more virulent or resistant pathogen was present and associated with outcomes.

5. Conclusion

Community acquired pneumonia is associated with high mortality in patients admitted to public ICUs in Brazil. The current findings demonstrate that co-morbidities and severity of illness are main drivers of mortality; however it also identifies potentially modifiable factors such as time to ICU admission. These findings highlights the needs to improve triage systems and resource allocation to allow early access to ICU.

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Conflicts of interest

Drs. Salluh is founder and equity holder at Epimed Solutions, the provider of a cloud-based healthcare analytics and performance evaluation software.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.11.024.

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