Mortality of Older Patients Admitted to an ICU: A Systematic Review

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Mortality of older patients admitted to an intensive care unit: a systematic review

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ABSTRACT

Objective: To conduct a systematic review of mortality and factors independently associated with mortality in older patients admitted to intensive care unit (ICU).

Data sources: MEDLINE via PubMed, EMBASE, the Cochrane Library and references of included studies.

Study selection: Two reviewers independently selected studies conducted after 2000 evaluating mortality of older patients (≥75 years old) admitted to ICU.

Data extraction: General characteristics, mortality rate and factors independently associated with mortality were extracted independently by two reviewers. Disagreements were solved by discussion within the study team.

Data synthesis: Because of expected heterogeneity, no meta-analysis was performed.
We selected 129 studies (median year of publication: 2015, interquartile range (IQR): 2012-2017) including 17 based on a national registry. Most were conducted in Europe and North America. The median number of included patients was 278 (IQR: 124-1068). ICU and in-hospital mortality were most frequently reported with considerable heterogeneity observed across studies that was not explained by study design or location. ICU mortality ranged from 1% to 51%, in-hospital mortality from 10% to 76%, 6-month mortality from 21% to 58% and 1-year mortality from 33 to 72%. Factors addressed in multivariate analyses were also heterogeneous across studies. Severity score, diagnosis at admission and use of mechanical ventilation were the independent factors most frequently associated with ICU mortality whereas age, comorbidities, functional status and severity score at admission were the independent factors most frequently associated with 3- 6 and 12 months mortality.

Conclusions: In this systematic review of older patients admitted to intensive care, we have documented a substantial variation in short and long-term mortality as well as in prognostic factors evaluated. Such variations warrant the development of ICU admission criteria for

older patients and of a core data set of prognostic factors to be evaluated in future studies by a multidisciplinary expert panel.

Introduction

Over the last two decades, the proportion of older patients (≥75 years old) admitted to intensive care units (ICUs) has significantly increased due to aging of the population (1, 2). The median age of ICU patients is above 65 years in many countries and the proportion of older patients is increasing faster than any other age group (3). Older patients are more often frail and represent a particular population because frailty may result in physical decline, comorbidities, polypharmacy and loss of functional autonomy (4–7). Reserve capacity is lower than in younger patients leading to an increased risk of mortality in the case of acute medical events or trauma. Older patients are more likely to develop sepsis, acute heart failure, or acute respiratory failure (8–11). Furthermore, these pathologies are usually more severe and more likely to result in secondary organ failure (8, 12). As a consequence, mortality rate is increased in this advanced age group (13). The benefit of ICU admission in this population is debated but validated triage tools to identify geriatric patients who are likely to survive high-intensity treatment are needed (14). A number of studies have analyzed factors associated with increased mortality in older patients admitted to ICU. Identification of these factors may be important to assist physicians in the triage process and to improve the care of older patients during and in particular after an ICU stay.

The aim of this study was to perform a systematic review of studies evaluating mortality of older patients admitted to an ICU and to describe factors independently associated with mortality.

Methods

This systematic review complies with the PRISMA Statement (15) and the protocol is registered in PROSPERO (CRD42019123548).

Search strategy

We searched MEDLINE via PubMed, EMBASE and the Cochrane library for relevant references using a dedicated search algorithm developed by a senior researcher, expert in systematic reviews and meta-analyses (AD) and adapted to each database (see Appendix 1 for search algorithm in PubMed). The search algorithms included keywords and free-text words for: 1) intensive care/critical care; 2) survival/mortality; 3) age ≥ 75 years and older. The search was first conducted in December 2018 and updated in February 2020.
Because observational studies can be registered at ClinicalTrials.gov(16), we also searched ClinicalTrials.gov for additional studies. Finally, we screened reviews on this topic and the list of references of each included study for any additional references.

Eligibility criteria of studies

We included studies

- for which at least 50% of the recruitment period was after year 2000. We focused on recent studies to avoid confounding with changes in clinical practice over time
- with a report in English
- including ICU patients ≥ 75 years in eligibility criteria or mean age ≥ 75 years in the main analysis or a subpopulation of older patients clearly identified with results reported separately. We chose 75 years as a cutoff because, even if there is no consensual definition of aging, this population is more comorbid (60% have at least 3

comorbidities vs 40% before 75 years old (5)) and more frail (20 to 35% vs less than 15% before 75 years (17)).

- reporting data on outcome in terms of survival/mortality among the following: ICU mortality, hospital mortality, 30-day mortality, 3-month mortality, 6-month mortality, 12-month mortality, > 12 month mortality.
- having a design clearly reported as retrospective or prospective cohort studies, with either single-center or multicenter recruitment, as well as national ICU registry-based studies.

Studies focusing on a specific population (e.g. patients with cancer) were eligible but were described separately.

We considered all studies evaluating mortality of older patients in ICU for any reason but we excluded studies conducted in specialized units such as coronary care units or neuro-vascular units.

We did not include studies reported as abstract only as data may be incompletely reported and because of difficulty in contacting authors.

Selection process

After removing duplicates, two reviewers independently evaluated each reference for eligibility based on title and abstract and, where necessary, on full-text. Any disagreements were resolved by discussion within the core study group to reach a consensus. Zotero (version 5.0, Center for History and New Media, George Mason University, Fairfax County, Virginia, United States) was used to deal with duplicates and to manage references.

Data extraction

Relevant data were collected using a dedicated data extraction form which was first tested on data retrieval from several studies. Subsequently, data were extracted independently by two reviewers. Any disagreements were resolved by discussion within the core study group to reach a consensus.

The following data were extracted: general characteristics of the study (year of publication, journal, country, setting), study design (prospective or retrospective cohort; single-center, multicenter or multinational recruitment), population characteristics (age, admission criteria), mortality at the different time-points available (number of events and number of patients analyzed) and prognosis factors analyzed in multivariate analyses of mortality and corresponding results (i.e. odds ratios, relative risks or hazard ratios with 95% confidence intervals, p values).

Short-term mortality is defined as ICU and hospital mortality. Long-term mortality is defined as 6 months and 1 year mortality.

If results were presented by subpopulation of patients, we collected information from all eligible subpopulations. Data on ICU structure like staffing, size of the unit, available resources or specific processes of care were not collected since such data were absent in most publications, including single center studies where this would have been most relevant.

Methodological quality assessment

The methodological quality of each study was evaluated using the CASP checklist for cohort studies (18).

Analysis

The characteristics of each included study were summarized. No meta-analysis was planned because of an expected heterogeneity due to variability across study design and population.

To describe results, we present forest plots for each key time-point. Because we expected heterogeneity, we planned the following pre-defined subgroups: according to study design (prospective or retrospective and single or multicenter studies),to geographical regions (if possible) and to admission criteria (elective or acutely admitted) if possible.

We also described factors evaluated in multivariate analyses for ICU mortality, in-hospital mortality and mortality at 6 and/or 12 months and reported those that were independently associated with mortality (defined as a p-value <0.05 or 95% confidence interval (CI) not including 1 in multivariate analysis). We grouped the factors in 3 categories: at baseline, on admission and during the ICU stay. Baseline factors included age, sex, comorbidities, functional status and frailty scores. Factors on admission included severity scores (as Acute Physiology And Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), Sepsis-related Organ Failure Assessment (SOFA)), type of admission, diagnosis at admission, Glasgow coma scale and biological factors (as creatinine, urea, lactate, C-reactive protein (CRP)). Factors during ICU stay included mechanical ventilation, use of vasoactive drugs, renal replacement therapy, ICU complications and limitation of therapy orders.

Forest plots were performed using R version 3.4.3 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Selection process

From 831 references retrieved by the search strategy and 23 additional studies identified from other sources, we retained 215 studies for full-text evaluation. After exclusion of a further 86 studies, 129 studies remained and were included in the final analysis (Figure 1) and a list of all included studies can be found in Appendix 3.

Characteristics of included studies

The median year of publication was 2015 (IQR: 2012-2017). Most studies were conducted in Europe (n=70, 54%) and North America (n=26, 20%). The study design was prospective in 52 studies (40%) and retrospective in 77 (60%). There was single-center recruitment in 77 studies (60%), multicenter recruitment within a single country in 42 (32%) and multinational recruitment in 10 (8%) studies. Seventeen studies (13%) were based on national registries. The funding source was reported in all studies with 36 (28%) declaring public funding and 81 (63%) no funding. Forty-three (33%) studies focused on a specific condition with sepsis being the most frequent (n=14). Most studies (n=88, 68%) included all types of admission (i.e. both emergency and planned) whereas 32 (25%) focused on emergency admission only. The inclusion criterion was an age of 75 years or more in 98 (76%) studies and the age threshold was 65 years old for the other studies. The median number of included patients was 278 (IQR: 124-1068) (Table 1). The methodological quality of included studies is described in Appendix 2.

Population characteristics

Seventeen studies presented outcome data separately for different subpopulations of patients resulting in a total of 147 subpopulations for subsequent analysis (one study described 3 subpopulations, the others, 2). Subpopulations were defined according to patient age in 11 studies, type of admission (i.e. emergency versus planned) in 2, time period in 1, length of

hospital stay (long vs short) in 1, specific medical condition (COPD vs. acute myocardial infarction vs. heart failure) in 1 and duration of spontaneous breathing test before extubation in 1. All the following results are based on these 147 subpopulations. Mean or median age was reported for 121 (82%) and ranged from 75 to 93 years old. Gender was reported for 127 (86%) and the proportion of men ranged from 24% to 87% (median 53%). Mean or median SAPS2 was reported for 42 and ranged from 15 to 71; mean or median APACHE II was reported for 62 and ranged from 11 to 68; mean or median SOFA was reported for 35 and ranged from 2 to 9. Charlson comorbidity score was reported for 58 and mean or median values ranged from 1 to 8 (Appendix 3).

Mortality

Mortality was reported at 1 month in 28 (19%) and at 3 months in 12 (8%) subpopulations. ICU mortality was reported for 99 (67%) subpopulations. Figure 2 shows ICU mortality by study design for the 64 not focusing on a specific condition and reporting sufficient data. ICU mortality varied greatly across studies: from 6% to 28% among multicenter prospective studies, from 6% to 28% among multicenter retrospective studies, from 6% to 51% for single-center prospective studies and from 1% to 51% for single-center retrospective studies. ICU mortality also varied greatly within the same continent (Appendix 4). We did not conduct subgroup analysis for emergency vs. planned admission because most studies did not report separate data according to the type of admission.

In-hospital mortality was reported for 104 (71%) subpopulations. Among the 66 not focusing on a particular condition and providing sufficient data, in-hospital mortality ranged from 11% to 42% among multicenter prospective studies, 12% to 44% among multicenter retrospective studies, 10% to 64% among single-center prospective studies and 19% to 76% among single-center retrospective studies (Figure 3).

Mortality at 6 months was reported for 15 (10%) subpopulations. Among the 10 not focusing on a particular condition and providing sufficient data, 6-month mortality ranged from 21% to 58% (Appendix 5). Mortality at 12 months was reported for 34 (23%) subpopulations. Among the 23 not focusing on a particular condition and providing sufficient data, 12-month mortality ranged from 33% to 72% (Appendix 5).

Factors associated with mortality

There was an evaluation of factors associated with mortality at different time points for 46 subpopulations (36%), with 10 concerning a specific condition. Of the 36 addressing a general situation, factors associated with ICU mortality were evaluated in 10. Severity score, diagnosis at admission and mechanical ventilation during ICU stay were the factors most frequently evaluated and associated with ICU mortality (Table 2 and Appendix 6).
Factors associated with in-hospital mortality were evaluated in 17 subpopulations. Of these, age, comorbidities, functional status and severity score at admission were the factors found to be most frequently associated with in-hospital mortality (Table 2 and Appendix 6).
Factors associated with mortality at 6 and/or 12 months were evaluated in 10 subpopulations. Age, comorbidities and severity score were also frequently retrieved as independent factors of mortality in this context (Table 3).

Discussion

In this systematic review, we report the largest overview to date on mortality rate of older patients admitted in ICU and factors associated with mortality. We included 129 studies conducted after year 2000, many being retrospective (60%) and single-center (60%). There were large variations across studies in terms of population characteristics and mortality rates. Short-term (ICU and hospital) mortality rate ranged from 1 to 76% and long-term (6-12 months) mortality rate from 21 to 72%. The prognostic factors most commonly identified included severity score and mechanical ventilation for short-term mortality and comorbidities, age and functional status for long-term mortality.

Our data reveals a very large variation in outcomes across studies, which does not seem to be completely related to the differences in study design. Several factors that could explain this variation are not covered in this study, since available information about structure and process were not reported in included studies, and also difficult to reveal in large multicenter studies.

Hence the variation in mortality rate may be explained by several factors:

A) Differences in admission policies resulting in different case mixes: It is likely that some centers have applied strict selection criteria on admission while other centers applied a lower threshold admitted more patients. There is no published recommendation regarding admission of older patients in the ICU (19) nor a broad consensus about who to admit to the ICU. A restrictive admission strategy could explain lower mortality because patients admitted in such centers may have better preserved activity levels, less frail and less comorbidity and/or organ dysfunction at baseline.

B) Differences in the intensity of treatment offered to older patients. Surprisingly few studies reports data on limitation of life-sustaining treatment that could affect the mortality rate substantially (20). There is some evidence of frequent non-formal

limitations of therapy applied to elderly patients in case of acute illness (21, 22), which may also affect outcomes of the included studies to a variable degree.

C) Organizational differences across countries, for instance whether patients are transferred from ICU to ward care or from hospital to nursing home for comfort care measures, which will affect the reported ICU or hospital mortality (20).

Factors associated with mortality are also very heterogeneous. Chronic health conditions were rarely reported and evaluated. Comorbidities were explored as factors potentially associated with outcome in only 6 studies for ICU mortality, 12 studies for hospital mortality and 10 studies for long-term mortality. Furthermore, several studies accounted for selected chronic medical conditions but did not use a validated comorbidity score such as Cumulative Illness Rating Scale (CIRS (23)) or Charlson Comorbidity Score. Functional autonomy was evaluated in 13 studies (for hospital and 6- and/or 12-month mortality) and frailty in 4 studies only. In non-ICU populations, these factors are shown to be associated with short and long-term mortality in older patients (4, 24). Furthermore, a recent meta-analysis concludes that frailty in ICU is associated with higher hospital and long term mortality and that frail patients are less likely to be discharged home (25). Improving the reporting of comorbidities and functional status as part of a comprehensive geriatric assessment (26) and evaluating frailty using validated scores could improve the baseline evaluation of critically-ill older patients in order to better estimate their prognosis. This would also allow standardization of potential prognostic factors to be evaluated in multivariate analysis to facilitate comparisons of results across studies and meta-analyses. In this context, it would be very useful to agree on a core data set to document at ICU admission in the very old using a collaboration between experts from different disciplines such as geriatrics, intensive care, emergency medicine, anesthesiology, surgery and general practice. The actual COVID-19 pandemic highlights the necessity to develop this core data set. Indeed, because of the severity of COVID pneumoniae

and the risk of health resource limitation, triage of older patients before ICU admission is even more necessary. The objective is to detect patients able to survive in good conditions and to give them a chance in ICU. Without clear and consensual admission criteria, there is a risk that age becomes the only criteria to refuse older patients ICU admission.

A formal geriatric assessment may be helpful for the decision-making process when admitting an older patient to ICU. However, this assessment is often impossible to conduct in an emergency context. As a strategy to improve the care of older patients, an ICU trial has been suggested (27) providing initial full organ support with continuous re-evaluation the next 48-72 hours. This strategy allows giving an equal chance to more patients, the time to collect all relevant information about medical history, functional status and potential advance directives, and to evaluate the progress under full treatment before deciding to continue or to withdraw treatment. This concept of a time-limited trial is particular appealing in the context of uncertainty (28, 29). Whether any of the included studies applied this strategy is however unknown and would also increase heterogeneity across studies.

The clinical trajectory of patients after ICU hospitalization is also important to consider in the context of long-term prognosis. After ICU discharge, many older patients often suffer from worsened comorbidities or secondary complications (pneumonia, swallowing disorders, neuromuscular dysfunction, delirium) and require early physical rehabilitation. All these elements are usually considered by geriatricians. In this context, creation of ICU networks involving both intensivists and geriatricians could be an option to improve patients´ care post-ICU and maybe their long term outcomes (30). Older patients frequently loose functional autonomy (31) and may develop neurocognitive disorders (32) after critical illness, which represent an additional burden also for relatives and caregivers (33). For all these reasons, older patients should ideally be followed up by geriatricians several months after ICU hospitalization. Whether any of the included studies are conducted in a multidisciplinary

environment including geriatric advice is largely unknown, although according to our information from real-life intensive care this is seldom done. This might also be another factor contributing to heterogeneity across studies.

The main limitation of our study is related to heterogeneity in population and design found in the reported studies precluding meta-analysis. Many studies are small single-center retrospective studies, which may be at higher risk of bias and have a limited generalizability. Most of the studies focused on short-term outcomes (ICU and hospital mortality) while ICU mortality might be influenced by end-of-life decisions and discharge policy. This is also true but to a lesser extent for hospital mortality. To overcome this limitation, we also reported long-term mortality assessed either at 6 months or 1 year after ICU admission. Age distribution is different across continents that may account for the low number of studies conducted in some parts of the world. Indeed, Europe is the continent where there is the higher proportion of people older than 75 years (8.7%), followed by North America (6.7%), Oceania (5.4%), South America (3.5%), Asia (3%) and Africa (1%) according to the United Nations (https://population.un.org/wpp/Download/Standard/Population/). Patient reported outcomes such as quality of life and functional status were missing in most included studies. Another important gap is related to structure and system factors that were almost never evaluated or reported in the included studies but that could play an important role in the observed mortality rates and evaluation of prognosis factors. Finally, because we relied on aggregated data and did not have access to individual patient data, it was not possible to exclude patients with a very short ICU length of stay related to post-operative surveillance. These patients may have a lower mortality.

This systematic review has revealed many shortcomings in included studies. This makes our understanding of the high mortality and morbidity in the elderly ICU patients fragmented with many areas of improvement. In particular the lack of information about pre-ICU conditions,

structure and system factors and of post-ICU trajectories with very few studies documenting non-mortality outcomes are reasons for concern.

Conclusion

In this systematic review of older patients admitted to the ICU, we have documented a large variation in short- and long-term mortality as well as in prognostic factors evaluated. Such variations clearly demonstrate our incomplete knowledge of the important factors, both patients related and system related, that leads to a high mortality in very old intensive care patients. There is still a lot of work to do in this particular field of critical care and researchers from different disciplines and across countries should cooperate to evaluate prognostic factors in future studies. It is important to have robust data about who most likely will profit from intensive care.

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Figure title and legends

Figure 1: Flow chart of the selection process

Figure 2: Forest plot of ICU mortality in included studies by study design

Figure 3: Forest plot of in-hospital mortality in included studies by study design

Table 1: General characteristics of included studies (N=129)

Characteristics	n (%)* N=129
Publication year, median (IQR)	2015 (2012-2017)
Location	
Europe	70 (54)
North America	26 (20)
Asia	13 (10)
Australia, New Zealand	8 (6)
South America	5 (4)
Other	7 (5)
Start year of recruitment, median (IQR)	2007 (2003-2011)
End date of recruitment, median (IQR)	2010 (2007-2013)
Study design	
Prospective	52 (40)
Retrospective	77 (60)
Study based on a national registry	17 (13)
Recruitment	
Single-center	77 (60)
Multicenter national	42 (32)
Multicenter international	10 (8)
Funding source	
Public	36 (28)
Private	3 (2)
Mixed funding	9 (7)
No funding	81 (63)
Condition	
All	86 (67)
Specific:	43 (33)
Sepsis	14 (11)
Mechanical ventilation	9 (7)
Medical condition only	3 (2)
Others	17 (13)
Type of ICU admission	
Emergency	32 (25)
Planned	2 (2)
Mixed	88 (68)
Not reported/unclear	7 (5)
Inclusion age	
≥75 years old	98 (76)
Other	28 (22)
Number of participants, median (IQR)	278 (124-1068)

*Results are expressed in median (IQR) or number (percentage). ICU: Intensive Care Unit. * Unless indicated otherwise*

Table 2: Factors associated with ICU and in-hospital mortality in included studies (studies on a specific condition are excluded).

Type of factor evaluated	Factor evaluated	n	Significantly associated (Yes/No)
ICU Mortality		**N=10**	
Baseline Status	Age	4	Yes in 2/4
	Sex	2	Yes in 1/2
	Comorbidities	6	Yes in 1/6
	Frailty score	1	Yes
Factors at admission	Severity score[¥]	13*	Yes in 8/13
	Type of admission	3	No in all
	Diagnosis at admission	10	Yes in 8/10
	Glasgow Coma Scale	1	Yes
	Biological factors §	5	Yes in 1/5
Factors during ICU stay	Invasive or non-invasive ventilation	6	Yes in 4/6
	Vasopressor use	2	No in all
	Renal replacement therapy	2	Yes in 1/2
	Weaning failure or re-intubation	2	Yes in 1/2
	Length of stay	1	Yes
	DNR	1	Yes
	ARDS	1	No
	Transfusion	1	No
	Positive blood culture	1	No
In-hospital Mortality		**N=17**	
Baseline Status	Age	10	Yes in 8/10
	Male sex	1	Yes
	Comorbidities	12	Yes in 10/12
	Functional status	9	Yes 6/9
	Frailty	2	Yes in all
Factors at admission	Type of admission (surgical or medical)	8	Yes in 5/8
	Severity score[¥]	16	Yes in 13/16
	Glasgow	4	Yes in all
	Diagnosis at admission	8	Yes in 6/8
	Biological factors[§]	6	Yes in 5/6
	Heart rate	1	Yes
	Mean Arterial Pressure	1	No
Factors during ICU stay	Mechanical ventilation	9	Yes in all
	Length of stay (hospital or ICU)	3	Yes in all
	Vasopressor	2	No in all
	Renal replacement therapy	1	Yes
	ICU acquired infection	1	Yes
	DNR	1	Yes
	Other	2	Yes in 1/2

Results are expressed in number. ICU: Intensive Care Unit, DNR: Do Not Resuscitate, ARDS: Acute Respiratory Distress. [¥]Include SOFA (Sepsis-related Organ Failure Assessment), APACHE (Acute Physiology And Chronic Health Evaluation) and SAPSII (Simplified Acute Physiology Score). [§]Include glucose level, blood urea nitrogen, creatinine level and CRP (C-Reactive Protein) Several severity scores were evaluated within the same study*

Table 3 : Factors associated with mortality at 6-12 months in included studies (studies on a specific condition are excluded) (N=10)

Type of factor evaluated	Factor evaluated	n N=10	Significantly associated (Yes/No)
Baseline Status	Age	8	Yes in 6/8
	Male sex	2	No in all
	Comorbidities	10	Yes in 9/10
	Functional status	4	Yes in all
	Frailty Score	1	Yes
Factors at admission	Type of admission	5	Yes in all
	Severity score[¥]	7	Yes in 6/7
	Glasgow	1	Yes
	Acute Renal Failure	2	Yes in all
Factors during ICU stay	Mechanical ventilation	2	Yes in all
	Septic complications	1	Yes
	DNR	1	Yes

Results are expressed in number. ICU: Intensive Care Unit, DNR: Do Not Resuscitate. [¥]Include SOFA (Sepsis-related Organ Failure Assessment) and SAPSII (Simplified Acute Physiology Score).