



RESEARCH

RETROSPECTIVE ANALYSIS OF COST AND FACTORS AFFECTING MORTALITY IN ELDERLY PATIENTS IN THE INTENSIVE CARE UNIT

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ABSTRACT

Introduction: The older population of the world continues to grow. Currently, 8.5% of people worldwide are above 65 years, leading to an increased frequency of intensive care unit admission. This study aimed to assess the cost and factors affecting mortality in elderly patients.

Materials and Methods: This retrospective cohort study included patients aged over 65 years admitted to the tertiary intensive care unit. The demographics including age, gender, body mass index, comorbidities, Glasgow coma scale scores, acute physiology and chronic health evaluation II, the Charlson comorbidity index scores, diagnosis, blood gas analysis results, type of mechanical ventilation, length of stay in the intensive care unit (ICU), time of death and cost of ICU stay were obtained from the government electronic mortality declaration system.

Results: This study evaluated 1401 patients with a mean age of 75.73 ± 6.92 , where the mean BMI was 25.31 ± 7.03 . Most of the patients ($n=714$, 51%) belonged to the 65–75 years old group while 569 (40.6%) belonged to the 75–85 years old group and 118 (8.4%) were over 85 years old. Mortality rates were the following: 28-day mortality rate, 41.7%; 1-year mortality rate, 66.4% and 2-year mortality rate, 75%. The mean cost of ICU stay was 7992.95 ± 10166.33 ₺, and the mean cost of hospital stay was 8211.28 ± 10172.41 ₺.

Conclusion: It is shown that comorbidities increased as age advanced, and sepsis remains the leading cause of death in short-term and long-term periods in the elderly population admitted to the ICU.

Keywords: Critical Care; Sepsis; Comorbidity; Mortality; Mechanical Ventilation; Aged.

INTRODUCTION

Technological advancements and improved health care resulted in increasing human lifespan. Therefore, the world population is progressively getting older. The admission of elderly and very elderly patients to the intensive care unit (ICU) has increased in developed countries (1). The short-term outcomes after ICU may be associated with illness severity, comorbidities, performance status of the patient and the quality of care. Despite previous studies, 'age' effect remains to be a debate where health-care professionals are still reluctant in admitting the elderly to the ICU (2). The severity of illness is the leading predictor of mortality rates in the ICU, ranging between 6.4 and 40% in different ICUs. Several studies focus on 30-day mortality, where 1-year and 2-year mortality rates seem to be more relevant. The discharge from the ICU of the elderly appears to be the beginning of the treatment strategy, since it is most likely crucial to hold the elderly outside of the ICU (3).

Moreover, ICU stay was seven times longer in patients above 75 years of age than in patients aged 65 years, and mechanical ventilation requirement was reported to be 10 times higher in patients over 85 years than in patients below 55 years (4,5). Besides the challenging medical care of the elderly, ICU cost accounts for 20–30% of hospital care costs. Several questions remain unanswered, such as the controversial benefit of ICU care for the elderly.

This study primarily aimed to evaluate the clinical characteristics and outcome in elderly patients, and the secondary goal was to define the independent predictors of ICU mortality. Lastly, particular focus was on medico-economic implications.

MATERIALS AND METHODS

This retrospective cohort study was approved by the Scientific Study Committee by a Health Sciences University Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee

(Date, 30.04.2019/ No: 066), and patients above 65 years admitted to the tertiary ICU between October 2014 and October 2016 were enrolled in this study.

Data

Patient's data were collected from the hospital database. Age, gender, body mass index (BMI), comorbidities, Glasgow coma scale (GCS) score, acute physiology and chronic health evaluation (APACHE) II scores, the Charlson comorbidity index (CCI) score, diagnosis, blood gas analysis results, type of mechanical ventilation (MV) applied in intensive care unit (invasive or noninvasive), length of ICU stay, time of death and cost of ICU stay were obtained from the government electronic mortality declaration system.

Statistical Analysis

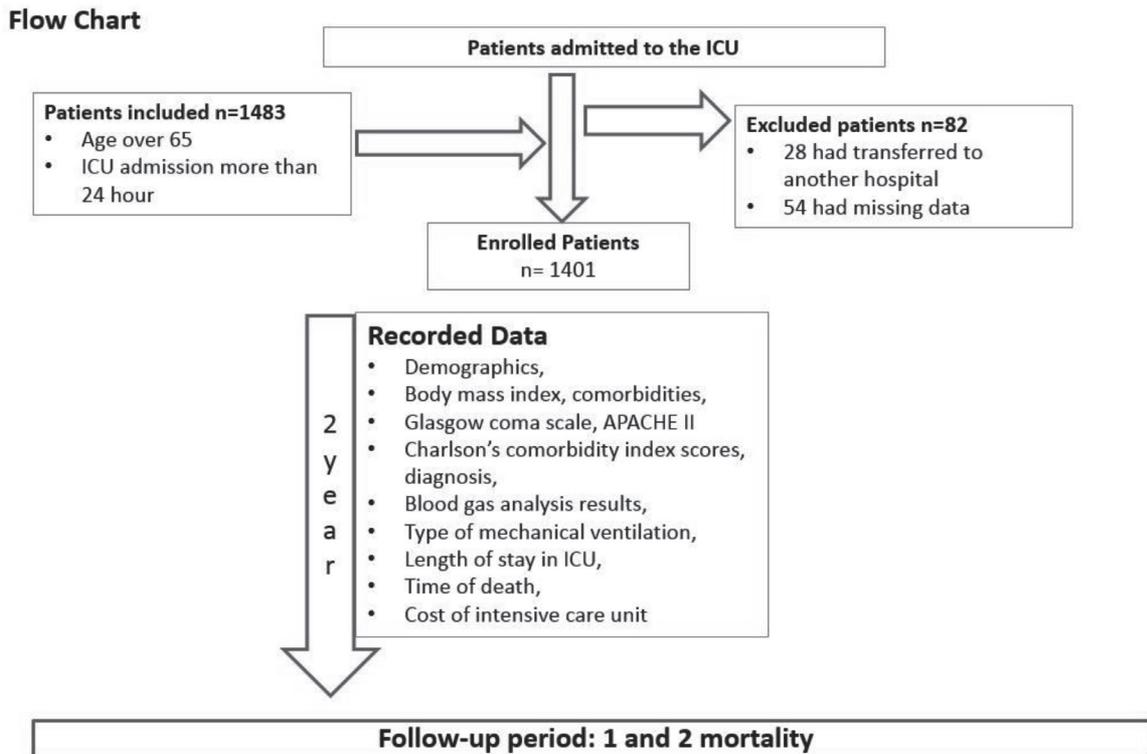
The distribution of the variables was analysed using Kolmogorov–Smirnov test, and the quantitative data were presented as mean and standard deviation where qualitative data were given as median (interquartile range [IQR] 25%–75%) values and also with numbers and percentage. The relationship between variables was determined using either Pearson (*r*) or Spearman's (*ρ*) correlation analysis. Long-term mortality risk factors were analysed by multivariate regression analysis, and the age groups and type of MV were compared by one-way ANOVA test. Intragroup comparisons were analysed using Tukey's HSD test. Independent samples t-test was used to compare the GCS, CCI and APACHE II scores. Categorical data was analysed using chi-square test. Data were statistically analysed using the Statistical Package for Social Sciences (SPSS) version 20 programme. The significance level was determined to be $p < 0.05$.

RESULTS

This study included 1401 patients. Figure 1 shows the recruitment of the patients. The mean age of the patients was 75.73 ± 6.92 , where the mean BMI



Figure 1. Flow chart of the study.



was 25.31 ± 7.03 . Most of the patients ($n=714$, 51%) belonged to the 65–75 years old group, while 569 (40.6%) belonged to the 75–85 years old group and 118 patients (8.4%) were over 85 years old. The diagnosis of the patients on admission were the following: pulmonary diseases ($n=1058$, 75.5%), cardiac diseases ($n=778$, 55.5%), renal diseases ($n=398$, 28.4%) and neurological diseases ($n=350$, 25%). Majority of the patients were referred from the emergency room (ER) ($n=705$, 50.3%), where chest disease was the second one ($n=581$, 41.5%). Table 1 presents the medical characteristics of the patients. The mean ICU stay was 9.63 ± 8.45 days, with a minimum of 1 and a maximum of 57 days.

The patients' mean survival time starting with the day admitted to the ICU was 374.31 ± 497.98 days with a minimum value of 1 and a maximum of 1935 days. A total of 497 (35.5%) of the patients died in the ICU, and 904 (64.5%) died after discharge. Table 2 shows the comparison of the GCS and APACHE II and CCI scores of patients who died in the ICU and after discharge. A positive weak correlation was detected between age and CCI score ($\beta=0.340$, $p<0.001$). The frequency of comorbidities among the age groups is shown in Table 3. A multivariate regression analysis of the age; presence of any of the comorbidities including pulmonary diseases (PD), cardiac diseases (CD), neurological diseases

Table 1. Characteristics of the patients.

	Mean±SD	Median	IQR
Age (years)	75.73±6.92	75	11
BMI (kg/m ²)	25.31±7.03	23	8
CCI score	5.45±1.62	5	2
APACHE II score	25.92±8.03	24	11
GCS score	12.29±4.24	15	4
	Hypoxia (n, %)	Hypoxia + Hypercarbia (n, %)	Metabolic disturbance (n, %)
Type of BGA	420 (30%)	826 (59%)	155 (11%)

BMI, body mass index; CCI, Charlson comorbidity index; APACHE, acute physiology and chronic health evaluation; GCS, Glasgow coma scale; BGA, blood gas analysis.

Table 2. APACHE II, CCI, and GCS score comparisons.

	Patients died in ICU	Patients died after discharge	p
APACHE II score	30.87±8.05	23.2±6.59	<0.001*
CCI score	5.98±1.78	5.16±1.44	<0.001*
GCS score	10.58±4.82	13.23±3.56	<0.001*

*p<0.05. Independent samples t test.

(ND), renal diseases (RD), malignancy, mechanical ventilation (no MV, NIMV or IMV), ARDS, sepsis, hypertension and diabetes mellitus as possible predictors of survival time starting from ICU admission to the time of death in the ICU; 28-day mortality; 1-year mortality and 2-year mortality is displayed in Table 4. A positive moderate correlation was noted between APACHE II score and ICU mortality, while a negative moderate correlation was observed between APACHE II score and survival time ($\rho=0.458$, $p<0.001$; $\rho=-0.461$, $p<0.001$, respectively). A positive weak was detected between CCI and ICU mortality, and a negative weak correlation was found between CCI and survival time ($\rho=0.232$, $p<0.001$; $\rho=-0.282$, $p<0.001$, respectively). Moreover, a

negative weak correlation was observed between GCS on admission and ICU mortality, while a positive weak correlation was noted between GCS on admission and survival time ($\rho=-0.318$, $p<0.001$; $\rho=0.354$, $p<0.001$, respectively). Table 5 displays the relationship between MV and age groups and scores. Mortality rates were found in the following order: 28-day mortality rate, 41.7%; 1-year mortality rate, 66.4% and 2-year mortality rate, 75%. Patients with MV had a mortality rate of 40.5% in 28 days, 62.5% in 1 year and 70.2% in 2 years. The costs of hospital and ICU stay according to age groups are summarised in Table 6. The mean cost of ICU stay was 7992.95 ± 10166.33 ₺, and the mean cost of hospital stay was 8211.28 ± 10172.41 ₺.



Table 3. The distribution of comorbidities among age groups.

	Total (n=1401) n (%)	65 – 75 years (n=714) n (%)	75 – 85 years (n=714) n (%)	> 85 years (n=714) n (%)	p
PD	1058 (75.5)	574 (80.4)	418 (73.5)	66 (55.9)	<0.001*
CD	778 (55.5)	361 (50.6)	337 (59.2)	80 (67.8)	<0.001*
ND	350 (25)	133 (18.6)	169 (29.7)	48 (40.7)	<0.001*
RD	398 (28.4)	172 (24.1)	178 (31.3)	48 (40.7)	<0.001*
Malignity	241 (17.2)	159 (22.3)	75 (13.2)	7 (5.9)	<0.001*
MV	1295 (92.4)	667 (93.4)	523 (91.9)	105 (89)	0.221
ARDS	39 (2.8)	24 (3.4)	11 (1.9)	4 (3.4)	0.262
Sepsis	384 (27.4)	182 (25.5)	171 (30.1)	31 (26.3)	0.185
DM	379 (27.1)	199 (27.9)	151 (26.5)	29 (24.6)	0.708
HT	785 (56)	373 (52.2)	331 (58.2)	81 (68.6)	0.001*

*p<0.05.

Chi-square test. PD, pulmonary diseases; CD, cardiac diseases; ND, neurological diseases; RD, renal diseases; MV, mechanical ventilation; ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; HT, hypertension.

Table 4. Multivariate regression analysis.

	Mortality in ICU (β, p)	28-days mortality (β, p)	1-year mortality (β, p)	2-years mortality (β, p)
Age (years)	–	0.038, 0.088	0.093, <0.001*	0.069, 0.007
PD	-0.106, <0.001*	-0.097, <0.001*	-0.055, 0.034*	-0.051, 0.059
CD	0.043, 0.044*	0.061, 0.008*	–	–
ND	–	0.061, 0.008*	0.123, <0.001*	0.095, <0.001*
RD	0.267, <0.001*	0.255, <0.001*	0.173, <0.001*	0.144, <0.001*
Malignity	0.120, <0.001*	0.128, <0.001*	0.185, <0.001*	0.160, <0.001*
MV	0.121, <0.001*	0.105, <0.001*	0.073, 0.002*	0.060, 0.018*
ARDS	0.051, 0.017*	0.054, 0.014*	–	–
Sepsis	0.365, <0.001*	0.351, <0.001*	0.241, <0.001*	0.191, <0.001*
DM	–	–	-0.045, 0.055	–
HT	-0.048, 0.028*	-0.076, 0.001*	–	–

*p<0.05. PD, pulmonary diseases; CD, cardiac diseases; ND, neurological diseases; RD, renal diseases; MV, mechanical ventilation; ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; HT, hypertension. Death in ICU: The model explained 62.1% of the variance (F=109.327, p<0.001).

28-days mortality: The model explained 61.4% of the variance (F=84.074, p<0.001). 1-year mortality: The model explained 47.6% of the variance (F=50.914, p<0.001). 2-years mortality: The model explained 38.7% of the variance (F=35.116, p<0.001).

acute respiratory distress syndrome; DM, diabetes mellitus; HT, hypertension.

Table 5. The effect of mechanical ventilation on the scores and survival time.

	No MV (n=106)	NIMV (n=516)	IMV (n=779)	P
65 – 75 years	47 (6.6%)	277 (38.8%)	390 (54.6%)	0.443
75 – 85 years	46 (8.1%)	192 (33.7%)	331 (58.2%)	
> 85 years	13 (11%)	47 (39.8%)	58 (49.2%)	
Stay in ICU (days)	5.34±4.99	7.26±5.19	11.79±9.81	<0.001*
Survival time (days)	557.3±551.14	576.35±533.44	215.38±399.86	<0.001*
GCS score	13.66±2.95	14.4±1.84	10.71±4.82	<0.001*
CCI score	5.37±2.04	5.14±1.44	5.67±1.63	<0.001*
APACHE II score	21.11±5.96	21.3±5.08	29.64±7.93	<0.001*

*p<0.05. One-way ANOVA test. Tukey's HSD test.

Intragroup comparisons for the stay in ICU: No MV-NIMV (p=0.066); No MV-IMV (p<0.001); NIMV-IMV (p<0.001).

Intragroup comparisons for survival time: No MV-NIMV (p=0.922); No MV-IMV (p<0.001); NIMV-IMV (p<0.001).

Intragroup comparisons for GCS score: No MV-NIMV (p=0.165); No MV-IMV (p<0.001); NIMV-IMV (p<0.001).

Intragroup comparisons for CCI score: No MV-NIMV (p=0.352); No MV-IMV (p=0.177); NIMV-IMV (p<0.001).

Intragroup comparisons for APACHE II score: No MV-NIMV (p=0.963); No MV-IMV (p<0.001); NIMV-IMV (p<0.001).

Table 6. The cost distribution according to the use of mechanical ventilation.

	No MV (n=106)	NIMV (n=516)	IMV (n=779)	P
Cost of Hospital Stay	4421.97±5130.9	6651.16±7824.3	9511.85±11459.14	<0.001*
Cost of ICU stay	4854.57 8460.27	5422.69±6245.22	9096.85±10692.66	<0.001*

*p<0.05. One-way ANOVA test. Tukey's HSD test.

Intragroup comparisons for cost of hospital stay:

No MV-NIMV (p=0.313); No MV-IMV (p=0.002); NIMV-IMV (p=0.001).

Intragroup comparisons for cost of ICU stay: No MV-NIMV (p=0.850); No MV-IMV (p<0.001); NIMV-IMV (p<0.001).

DISCUSSION

This study showed that PD, CD and HT are the leading cause of ICU admission among the elderly population, where CD, ND, RD and HT have increased with the advancing age and PD and malignancy decreased. The evident causes of death in the ICU appears to be RD and sepsis, those are the same in 28-days. Moreover, 1-year and 2-year mortality were considerably associated with sepsis, RD and malignancy in the elderly population

in the ICU. Patients with NIMV had a longer survival compared to patients with IMV or without MV. However, MV (NIMV or IMV) lengthened ICU stay and increased the cost of hospital and ICU stay. It is also detected that higher APACHE II score was associated with increased ICU mortality rate and longer survival time. Life expectancy has increased in the developed countries, raising the number of ICU admissions. The prognosis prediction of the elderly in the ICU has been investigated by sev-



eral studies, including that of Somme et al. that showed the intensity of the illness evaluated by APACHE II score could be the most important predictor in short-term mortality in elderly patients. The authors also reported that age and limited daily activities might be the possible predictors of the long-term mortality (5). Several studies reported the same result; that is, severity of the illness was the only predictor for short-term mortality (1,6,7). Despite the abovementioned studies, recent analysis conducted on large populations demonstrated that the medical condition of the patient in the hospital is more likely associated with in-hospital death rather than age (8). Moreover, Flaatten et al. showed that age had a minimal effect on ICU survival (9). This study revealed that considering the age as a single variable in the equation could be an underestimation compared to the condition of the patient associated with diseases they had. However, age is a factor indirectly affecting the observed frequency of the disease, leading a change on the balance by a path that did not exist in the account. Studies have demonstrated that ageing is associated with an increased susceptibility to PD (10,11). Despite the study's limited sample population, it was shown that PD and malignancy frequency decreased related to advancing age. This outcome could be associated with the low number of patients > 85 years of age, which might be higher than the sum of the patients in the 75–85 years and > 85 years groups. In contrast, advanced age is evidently related to malignancy. This is also confirmed by the present study (11). Inevitably, life expectancy is shorter in a patient diagnosed with cancer who also requires ICU treatment associated with accompanying disorders, and age is also related to prolonged MV in the elderly (12).

Furthermore, physiologic changes may occur in the cardiovascular system of elderly patients. Stage 1 diastolic dysfunction is a normal alteration of ageing. Left ventricular outflow may be depleted under stress conditions by a change in the structural integrity of the ventricular space called

'sigmoid septum'. Ageing leads to reduced maximal cardiac output; decreased inotropy, lusotropy and chronotropy and lower tissue extraction of oxygen (13). Renal changes are mainly caused by the decreased extraction of sodium levels, triggering older patients to be more prone to volume fluctuations. Diminished baroreceptor sensitivity is also a negative factor for pressure control of the cardiovascular system. Moreover, ageing affects cognitive functions, resulting in difficulty in memory, executive functioning and processing speed. Immobility is another loss of functioning during ageing observed in 82% of the patients above 85 years. Immobility and sedentary lifestyle impair the physiologic changes on other systems. It is noted that early mobility and physical exercise are fundamental in improving the functionality of the elderly patients (14-16). This study demonstrated that the frequencies of CD, ND, RD and HT increased with advancing age, also noted in previous studies mentioned above.

Nevertheless, the overall ICU mortality was affected by sepsis, a known cause of death which is the most likely cause of admission and the most common cause of death in the ICU and has been currently indicated as the final common route to death from infection (17). It has a high mortality rate ranging from 11.9% to 47.2% (18). In this study, sepsis had the single factor associated with the overall, 28-day, 1-year and 2-year mortality with a higher correlation coefficient than the other variables including RD and malignancy. Despite the development of detailed sepsis guidelines for those requiring early diagnosis and prompt administration of therapy to prevent single- or multiple-organ dysfunctions, sepsis remains to be the most challenging syndrome worldwide. Recent developments in the management of sepsis have decreased mortality rates by 20 to 30% in the last decades; however, complexity of therapy for sepsis results in high costs (19-21). Moreover, the treatment of elderly patients admitted to the ICU could be challenging due to various factors. This

group of patients has a lower life expectancy, high mortality rates and high health-care costs, increasing with advancing age. In this study, the mortality rates were 41.7%, 66.4% and 75% in 28-day, 1-year and 2-year mortality, respectively. Higher mortality rates indicated that the severity of comorbidities accompanying complications in ICU could increase with advancing age. The bigger percentage of patients admitted to the ICU was comprised of elderly patients above 75 years. The use of recent technologies, which are also expensive, is increasing and expands the health-care costs accompanied by increased ICU admission (22).

The use of MV holds higher ICU costs (23). Similar to this information, this study showed that MV requirement extends the ICU and hospital stay that also increase cost. An interesting finding of this study is that MV seemed to shorten survival time; however, MV is a technique performed in respiratory failure. The lower survival time may be considerably associated with the severe comorbidities leading to the use of MV. Several studies have been conducted on the prediction of ICU mortality, resulting in a highly valuable scoring system called APACHE II (22). The relationship between APACHE II score and mortality and survival time in elderly patients is a known condition in which the APACHE II score defines the patient's mortality risk on admission.

REFERENCES

1. Martin-Loeches I, Guia MC, Vallecocchia MS et al. Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: a prospective, observational, multicenter cohort study. *Ann Intensive Care* 2019; 9 (1): 26. (PMID:30715638).
2. Zampieri FG, Colombari F. The impact of performance status and comorbidities on the short-term prognosis of very elderly patients admitted to the ICU. *BMC Anesthesiol* 2014; 14: 59. (PMID:25071415).
3. Le Borgne P, Maestraggi Q, Couraud S et al. Critically ill elderly patients (≥ 90 years): Clinical characteristics, outcome and financial implications. *PLoS One* 2018; 13 (6): e0198360. (PMID:29856809).
4. Dinkci MD, Yuze Y, Cevik B, Erkal KH. Retrospective analysis of factors affecting intensive care unit mortality in patients over 75 years of age. *Turkish Journal of Geriatrics* 2017;20 (2): 91-99.
5. Somme D, Maillet JM, Gisselbrecht M, Novara A, Ract C, Fagon JY. Critically ill old and the oldest-old patients in intensive care: short- and long-term outcomes. *Intensive Care Med* 2003; 29 (12): 2137-2143. (PMID:14614546).
6. de Rooij SE, Abu-Hanna A, Levi M, de Jonge E. Factors that predict outcome of intensive care treatment in very elderly patients: a review. *Crit Care* 2005; 9 (4): R307-314. (PMID:16137342).

Overall, this study showed the causes of ICU death by utilising the elderly population, the association between the advanced age and comorbidities and the effects of MV on the ICU stay and cost. These data provide baseline and local information that might be enhanced by gathering data from distinct hospitals and regional areas.

This study had some limitations. First, the blood gas analysis data could be obtained in detail provided there is additional information on the patient's condition; unfortunately, we were not able to obtain such data from the hospital database. Second, our data did not include the patient's functional status after discharge. Third, the admission policy variation across countries may lead to restrict the generalizability of the results.

Therefore, this study revealed that comorbidities increased along with advancing age, and sepsis is still the leading cause of death in short-term and long-term periods in the elderly population admitted to the ICU. Further studies with large sample size may be conducted to elucidate this outcome.

CONFLICT OF INTEREST

All authors declared that there is no conflict of interest.



7. Vosylius S, Sipylaite J, Ivaskevicius J. Determinants of outcome in elderly patients admitted to the intensive care unit. *Age Ageing* 2005; 34 (2): 157-162. (PMID:15713860)
8. Boumendil A, Angus DC, Guitonneau AL et al. Variability of intensive care admission decisions for the very elderly. *PLoS One* 2012; 7 (4): e34387. (PMID:22509296)
9. Flaatten H, De Lange DW, Morandi A et al. The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (≥ 80 years). *Intensive Care Med* 2017; 43 (12): 1820-1828. (PMID:28936626).
10. Guidet B, Leblanc G, Simon T et al. Effect of Systematic Intensive Care Unit Triage on Long-term Mortality Among Critically Ill Elderly Patients in France: A Randomized Clinical Trial. *JAMA* 2017; 318 (15): 1450-1459. (PMID:28973065).
11. Vaz Fragoso CA. Epidemiology of Lung Disease in Older Persons. *Clin Geriatr Med* 2017; 33 (4): 491-501. (PMID:28991646)
12. Ely EW, Wheeler AP, Thompson BT, Ancukiewicz M, Steinberg KP, Bernard GR. Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. *Ann Intern Med* 2002; 136 (1): 25-36. (PMID:11777361).
13. Jackson CF, Wenger NK. Cardiovascular disease in the elderly. *Rev Esp Cardiol* 2011; 64 (8): 697-712. (PMID:21723657).
14. Deary IJ, Corley J, Gow AJ et al. Age-associated cognitive decline. *Br Med Bull* 2009; 92: 135-152. (PMID:19776035).
15. Axer H, Axer M, Sauer H, Witte OW, Hagemann G. Falls and gait disorders in geriatric neurology. *Clin Neurol Neurosurg* 2010; 112 (4): 265-274. (PMID:20089351).
16. Groessl EJ, Kaplan RM, Rejeski WJ et al. Physical Activity and Performance Impact Long-term Quality of Life in Older Adults at Risk for Major Mobility Disability. *Am J Prev Med* 2019; 56 (1): 141-146. (PMID:30573142).
17. Perner A, Gordon AC, De Backer D et al. Sepsis: frontiers in diagnosis, resuscitation and antibiotic therapy. *Intensive Care Med* 2016; 42 (12): 1958-1969. (PMID:27695884).
18. Sakr Y, Jaschinski U, Wittebole X et al. Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. *Open Forum Infect Dis* 2018; 5 (12): ofy313. (PMID:30555852).
19. Rhodes A, Evans LE, Alhazzani W et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017; 43 (3): 304-377. (PMID:28101605).
20. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013; 41 (5): 1167-1174. (PMID:23442987).
21. Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. *Intensive Care Med* 2017; 43 (5): 625-632. (PMID:28130687).
22. Reyes JC, Alonso JV, Fonseca J, Santos ML, Jiménez Mde L, Braniff J. Characteristics and mortality of elderly patients admitted to the Intensive Care Unit of a district hospital. *Indian J Crit Care Med* 2016; 20 (7): 391-3977. (PMID:27555692).
23. Milbrandt EB, Eldadah B, Nayfield S, Hadley E, Angus DC. Toward an integrated research agenda for critical illness in aging. *Am J Respir Crit Care Med* 2010; 182 (8): 995-1003. (PMID:20558632).