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Serum albumin is a strong predictor of sepsis outcome in elderly patients

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Abstract:	<p>Background The incidence of sepsis is disproportionately higher in elderly adults, and age is an independent predictor of mortality.</p> <p>Design Retrospective analysis was conducted among patients admitted to the emergency department in a tertiary teaching hospital from January 2016 to June 2017.</p> <p>Objectives To study the prognosis determinants of sepsis among elderly patients attended in the emergency room of a tertiary care hospital. As secondary objectives we aimed to describe the causes of sepsis, the general outcome and the general characteristics of these patients.</p> <p>Results Two hundred- and thirty-five-episodes data of patients admitted throughout the 15-month study period that were diagnosed of sepsis, severe sepsis or septic shock were included. Throughout the study cohort, 51 patients (21.7%) fulfilled the criteria of severe sepsis or septic shock. All-cause mortality was 11 patients (4.7%) on day 14 and 27 (11.5%) on day 30. Prognosis factors associated with 30-day mortality were: albumin level <2.6 g/dl (first quartile of the overall population) Odds Ratio (OR) 3.26,95% CI:12-9.41;p=0.029), Charlson comorbidity index (OR 1.23,95%CI:1,04-1,45; p=0.012),C-Reactive Protein on admission OR 1.04 95%CI:0.99-1.08;p=0.062) and non-adequacy of the initial antimicrobial therapy OR:3.3, 95%CI:1.06-10.4;p=0.039).</p> <p>Conclusion Among elderly patients with sepsis, strong predictors of mortality such as albumin could be considered as part of prognosis and future potential interventions. Adequacy of antimicrobial therapy at admission must be one of the objectives in the treatment of</p>

	sepsis, also in the elderly, since it is an independent predictor of mortality.
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Serum albumin is a strong predictor of sepsis outcome in elderly patients

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Abstract (Word count 245 words)

Background

The incidence of sepsis is disproportionately higher in elderly adults, and age is an independent predictor of mortality.

Design

Retrospective analysis was conducted among patients admitted to the emergency department in a tertiary teaching hospital from January 2016 to June 2017.

Objectives

To study the prognosis determinants of sepsis among elderly patients attended in the emergency room of a tertiary care hospital. As secondary objectives we aimed to describe the causes of sepsis, the general outcome and the general characteristics of these patients.

Results

Two hundred- and thirty-five-episodes data of patients admitted throughout the 15-month study period that were diagnosed of sepsis, severe sepsis or septic shock were included. Throughout the study cohort, 51 patients (21.7%) fulfilled the criteria of severe sepsis or septic shock.

All-cause mortality was 11 patients (4.7%) on day 14 and 27 (11.5%) on day 30. Prognosis factors associated with 30-day mortality were: albumin level <2.6 g/dl (first quartile of the overall population) Odds Ratio (OR) 3.26,95% CI:1.2-9.41;p=0.029), Charlson comorbidity index (OR 1.23,95%CI:1.04-1.45; p=0.012),C-Reactive Protein on admission OR 1.04 95%CI:0.99-1.08;p=0.062) and non-adequacy of the initial antimicrobial therapy OR:3.3, 95%CI:1.06-10.4;p=0.039).

Conclusion

Among elderly patients with sepsis, strong predictors of mortality such as albumin could be considered as part of prognosis and future potential interventions. Adequacy of antimicrobial therapy at admission must be one of the objectives in the treatment of sepsis, also in the elderly, since it is an independent predictor of mortality.

Introduction

Ageing is a heterogeneous process among individuals with different physiological response. There is a functional and repair capacity impairment. Infection and the altered response of the immune system in the elderly leads to an uncommon form of severe infection or sepsis (1,2). Making of sepsis a life-threatening clinical condition which involves a profound systemic response to infection and results in serious, often irreversible, damage to cells and tissues (2,3). However, severe infection sometimes has atypical presentation in the elderly making its recognition difficult and worsening prognosis (4).

The incidence of sepsis is disproportionately higher in elderly adults, and age is an independent predictor of mortality. Compared with younger patients with sepsis, elderly non-survivors of sepsis died earlier during hospitalization and elderly survivors presented great disability after the process (4). Since this form of severe infection could have strong influence in prognosis of elderly patients, we aimed to study the determinants of sepsis outcome among elderly patients attended in the emergency room of a tertiary care hospital. As secondary objectives we aimed to describe the causes of sepsis, the general outcome and the general characteristics of these patients.

Patients and Methods

Design

A retrospective analysis was conducted among patients admitted to the emergency department (ED) of a tertiary teaching hospital in Barcelona from January 2016 to June 2017. All adult in-patients aged >65 years old with ICD-9 codification at discharge report for sepsis or septic shock (995.9X, 038.xx, 785.52) were included.

Clinical variables

Data on demographic characteristics, comorbidities, microbiology, severity of illness at presentation was qualified by APACHE2, presence of systemic inflammatory response syndrome (SIRS) criteria (5) and quick-SOFA (6).

Information on the clinical and analytical presentation of infection was also collected at day 0 (when the infection was suspected). This was possible due to the standardization of the blood analysis when sepsis is suspected in our hospital.

Levels of albumin were classified as marked hypoalbuminemia (<2.6 mg/dL), mild hypoalbuminemia (2.7-3.5 mg/dL), normal albumin (3.5-4.5 mg/dL).

Additional information about the infection such as the aetiology, initial treatment, adequacy of empirical antimicrobial therapy (considered when an active antimicrobial agent was administered at the recommended dose), intensive care unit (ICU) admission, and microbiology results were also recorded.

Pathogens were considered multidrug-resistant (MDR) if they showed acquired non-susceptibility to at least one agent in three or more antimicrobial categories/families.

As principal outcome the role of inflammatory and nutritional markers as mortality predictors. Other secondary outcomes variables were the rate of 30-day mortality.

The present study was conducted in accordance with the principles stated in the Declaration of Helsinki and was approved by the local ethical committee.

Statistical analysis

Univariate analyses were performed using the Chi-square test or Fisher's exact test and the Student's t-test and Mann–Whitney U-test for comparison of categorical and continuous variables, respectively.

An exploratory multivariate analysis for analyzing predictors of in-hospital death at 30-day was performed. Multivariate analyses were performed by logistic regression.

The variables introduced in the logistic regression model were: Albumin levels at admission, CRP, Charlson comorbidity index, severe sepsis or shock, qSOFA >2 at admission, APACHE2 at admission, SIRS criteria at admission, inadequate empirical treatment, infection produced by a multiresistant bacteria. Along with other variables associated with mortality in a conservative univariate analysis at a level of significance of <0.2. Variables were selected using a backward stepwise process; a p-value of <0.1 was used to delete variables in subsequent steps. Interactions between empirical treatment and MDR bacteria, SIRS and qSOFA were also studied. All analyses were carried out using Stata 14.0 I/C software package (Stata, Houston, TX, US).

Results

Baseline characteristics

Two hundred and thirty five episodes data of patients admitted throughout the 15-month study period were included. Table 1 shows baseline characteristics. Regarding the infection acquisition sites, 169 (71.9%) community acquired infections, 36 (15.3%) were in-hospital acquired and 30 (12.8%) healthcare related infections.

The most frequent sources of infection were urinary 126 patients (53.6%), respiratory 62 patients (26.4%) and intraabdominal 27 patients (11.5%).

Above all the microbiological test performed, blood cultures were positive in 99 patients (44%).

The most common isolated microorganism was *Escherichia coli* in 100 episodes (42.6%), being 23 (23%) producers of Extended spectrum beta-lactamases (ESBL) and representing 10% of total microbiological isolations. This was followed by *Klebsiella pneumoniae* isolates in 16 episodes (6.8%) being 4 of them (1.7% of the total) ESBL producers.

According to these results, empirical antimicrobial treatment was adequate in 196 patients (83.4%) of episodes. Non-adequate antimicrobial treatment was significantly higher in the non-survival group (14% vs 34%; p=0.013).

All-cause mortality was in 11 patients (4.7%) on day 14 and 27 (11.5%) on day 30.

Variables associated with 30-day mortality

The results of the univariate analysis of the epidemiological, clinical and laboratory factors associated with all-cause 30-day mortality in elderly patients with sepsis are described in table 1 .

No differences were observed in the frequency of MDR pathogens between survivors and dead patients (33 (15%) and 3 (11%), $p=0.504$ respectively.

APACHE2 at admission was significantly higher in patients who died compared to those who survived (15 vs 12; $p<0.001$), respectively.

After a backward stepwise variable selection logistic regression showed that variables independently associated with 30-day mortality were (table 2): albumin level <2.6 g/dl (first quartile of the overall population) odds ratio (OR) 3.26, 95% CI: 1.2-9.41; $p=0.029$), Charlson comorbidity index (OR 1.23, 95% CI: 1.04-1.45; $p=0.012$), PCR on admission OR 1.04 95%CI: 0.99-1.08; $p=0.062$) and non-adequacy of the initial antimicrobial therapy OR: 3.3, 95%CI: 1.06-10.4; $p=0.039$)

Discussion

We report that prognosis elderly patients with sepsis is determined by patients' comorbidity, the concurrence of shock or severe sepsis, the prior nutritional status measured by serum albumin levels at admission and importantly the adequacy of antimicrobial therapy and the prior nutritional status measured by albumin levels at admission.

Though prior reports have described the association between hypoalbuminemia and mortality in conditions such stroke, myocardial infarction or hip fracture (14-18). Data available about albumin at admission and sepsis outcomes are scarce. In our series, low albumin levels on admission remained independently associated with mortality risk even when adjusting by known risk factors for increased mortality, including gender, age, smoking, alcohol, and comorbidities.

Albumin levels reflect the nutritional status, organic function or prior physical activity of patients. However, the underlying inflammation status through increased interleukin-1 or tumour necrosis factor, induce the decrease of albumin production by the liver (1,7,19) being co-responsible of the hypoalbuminemia seen since the early stages of sepsis.

Additionally, as hypothesis for the impact of albumin in infection prognosis is the fact that pharmacokinetics of antimicrobials could be altered by hypoalbuminemia (i.e.free plasma levels antibiotics with high protein bounding could be significantly decreased due to an increased elimination) impairing antimicrobial levels in patients with low albumin. Since albumin levels on admission seem to be an important predictor of mortality in our cohort, further studies should be carried out to unveil this association.

In our series non-adequacy of initial treatment on admission is independently associated with mortality, which has also previously reported (20). In the same line, Leibovici et al. found decreased crude mortality rate among patients with bacterimia and septic shock when empiric treatment was adequate (21). However, all these studies have in common that the population selected were

young people with sepsis and, to our knowledge, no extensive large studies focused in elderly have been performed (20,21,22).

Noteworthy, similarly to other studies we found a poor performance of the qSOFA score amongst our series. Askim et al. found that qSOFA failed to be a good risk stratification tool to predict the 7-day and 30-day mortality (11). Probably qSOFA score should be used cautiously in the elderly population, at least until it will be prospectively validated.

Our study has several limitations, first this is a retrospective design basing data on electronic chart review have limited information, and some variables could not be controlled. Second, we did not have information regarding the baseline nutritional status of the patients, other than albumin levels. Hence, taking into account the observational design of the study, causation cannot be established.

In conclusion, the elderly population is an heterogeneous group where clinical presentation of severe infection presents a wide range of clinical pictures. Strong predictors of mortality such as albumin could be considered as part of prognosis and potential interventions. Adequacy of antimicrobial therapy at admission must be one of the objectives in the treatment of sepsis, also in the elderly, since it is an independent predictor of mortality.

Acknowledgement

IAB, RGF, SL, LS, OV, RM designed the study. IAB, RGF collected data. RGF, IAB did the statistical analysis. RGF, IAB, SL, LS prepared the manuscript. IAB, RGF, SL, LS, OV, RM reviewed the manuscript.

Compliance with Ethical Standards:

This study had no funding. No conflict of interest was reported by any of the authors. This study was submitted and approved by the IRB. No informant consent was needed.

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Table 1

	Overall	Survivors (n=208)	Non-survivors (n=27)	P-value
Age (years, median, IQR)	75 (71-82)	75 (71-81)	77 (73-85)	0.593
Male n (%)	138 (58%)	122 (88%)	16 (12%)	0.954
Female n (%)	97 (42%)	86 (88%)	11 (12%)	0.954
Charlson Comorbidity Index median (IQR)	3 (1-6)	3 (1-6)	6 (2-8)	0.01
Cognitive impairment n (%)	51 (21%)	46/208 (22%)	5/27 (19%)	0.670
Atrial Fibrillation; n (%)				
Ischemic Heart Disease: n (%)	43 (18%)	37/208 (17%)	6/27 (22%)	0.575
Congestive Heart Failure; n (%)	26 (11%)	20/208 (9%)	6/27 (22%)	0.049
Cerebrovascular disease; n (%)	27 (11.5%)	24/208 (11%)	3/27 (11%)	0.948
COPD; n (%)	70 (29%)	61/208 (29%)	9/27 (33%)	0.668
Alcohol abuse; n (%)	9 (4%)	8/208 (4%)	1/27 (4%)	0.971
Chronic renal failure; n (%)	41 (17%)	32/208 (15%)	9/27 (33%)	0.021
Diabetes Mellitus; n (%)	104 (44%)	92/208 (44%)	12/27 (44%)	0.983
Clinical presentation				
Typical	183 (77%)	162/208 (77%)	21/27 (77%)	0.990
Acute mental status deterioration	59 (25%)	52/208 (25%)	7/27 (25%)	0.917
Fever (>38 C); n (%)	122 (52%)	107/208 (51%)	15/208 (55%)	0.705
Hypotension; n (%)	60 (25%)	54/208 (74%)	6/27 (22%)	0.675
C-Reactive Protein Median mg/dl (IQR)	12 (6-23)	12 (5-23)	19 (8-25)	0.014
Procalcitonin ng/ml, Median (IQR)	4.1 (0.47-27.05)	3.2 (0.35-23.2)	7.87 (4.9-47.92)	0.836
Albumin g/dl, median (IQR)	3 (2.6-3.3)	3.1 (2.7-3.4)	2.6 (2.45-2.85)	<0.0001
Bloodstream infection; n (%)	99 (44%)	85/208 (41%)	14/27 (52%)	0.277
MDR infection; n (%)	36 (15%)	33/208(16%)	3/27(11%)	0.519
Appropriate treatment at admission; n (%)	196 (83%)	178/208 (86%)	18/27 (66%)	0.013
APACHE2 at admission, median (IQR)	12 (9-16)	12(9-16)	16(12-19)	0.0001
ICU Admission n (%)	34 (14%)	29/208 (14%)	5/27 (18%)	0.532
SIRS≥2	153 (65%)	134/208 (64%)	19/27 (70%)	0.372
qSOFA ≥2	58 (24%)	51/208(24%)	7/27 (26%)	0.873

Table 1. Baseline characteristics of elderly patients with sepsis. Univariate analysis comparing

survivors and non-survivors.

Table 2

	OR	95 IC	p-value
Albumin <2.6g/dl	3.26	1.12-9.41	0.029
Charlson Index	1.23	1,04-1,45	0,012
C-RP	1,04	0,99-1,08	0,062
Adequate initial treatment	3,37	1,06-10,4	0,039

Table 2. Multivariate analysis of 30-day mortality in sepsis in the elderly. C-RP C Reactive Protein. Albumin <2.6g/dl (low value IQR)