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ORIGINAL ARTICLE

Attenuation of the physiological response to infection on adults over 65 years old admitted to the emergency room (ER)

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Abstract It has been considered that the elderly have clinical manifestations different from the ones observed in middle-age adults during an injury event. This hypothesis has not been extensively explored in sepsis and bacterial infections. Secondary analysis of two prospective studies including 2611 patients over 18 years of age admitted to the emergency room with confirmed or probable bacterial infections and sepsis. The outcome measures were heart rate, respiratory rate, systolic blood pressure, temperature, Glasgow Coma Scale, creatinine, PaO_2/FiO_2 and platelets daily during the first week. Compared to survivors younger than 65, the deceased under 65 had an average heart rate of 12.5 beats per minute per day higher (95% CI 9.32; 15.61), while patients over 65 who died barely had an average 5.7 beats per minute per day higher than the same reference group (95% CI 3.45; 8.06). The systolic blood pressure had a significant decreased in those who died younger than 65, compared to survivors with the same age, in both cohorts (−5.2 mmHg, 95% CI −8.17; −2.23 and −8.5 mmHg, 95% CI −13.48; −3.54, respectively), while those older than 65 who died had a nonsignificant increase (+1.6 mmHg, 95% CI −1.33; 4.62 and +0.1, 95% CI −6.48; 6.72, respectively) compared to the same reference group. The behavior of most clinical and laboratory variables suggests a less pronounced response of subjects above 65 years of age who died 28 days after being diagnosed with sepsis.

Keywords Elderly · Sepsis · Physiology · Infection

Introduction

Severe sepsis and septic shock are among the main causes of death in the world and the most common cause of death of critically ill patients at noncoronary ICUs [1]. In the USA, the yearly cost for care of these patients is about US$14 billion [2], highlighting their importance for health care. However, death rates vary depending on patients' characteristics, type of infection and severity, with 28-day rates ranging from 10 to 40% [3–5]. Some criteria have been proposed to identify sepsis, severe sepsis and septic shock in an attempt to identify on time those patients who are more affected for starting adequate treatment [6, 7]. These criteria are essentially supported on clinical and laboratory findings that represent a biological response to infection, under the premise that higher intensity in that response is also a reflection of severity.

On the other hand, it has been established that individuals in extremes in age would have different clinical manifestations from those observed on middle-age adults, in the event of any injury. Particularly, the elderly's

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physiology seems to explain certain differences in vital signs and physical findings compared to young or middle adults [8, 9]. These characteristics have recently allowed to conclude that the vital signs of patients under 65, in comparison with people over 65, help to identify more accurately the risk of cardiac arrest [10]. Nevertheless, regarding severe bacterial infections and sepsis, recent research just seems to refer to the differences in age-related molecular and immunological changes [11–13]. We believe that the clinical behavior of sepsis is also different on elderly patients and that it is possible to identify differences depending on age and final prognostic.

Our objective was to determine whether there are different trends in vital signs and in basic laboratories at admission to the ER and during the first week of hospitalization, in patients over or under 65 years of age with diagnosis of sepsis or severe bacterial infection, according to their vital status on day 28.

Materials and methods

Study design and setting

This is a secondary analysis of two prospective studies, EPISEPSIS Colombia [5] and DISEPSIS [14]. The former was conducted for 6 months in nine public and private institutions to define the epidemiology of sepsis in Colombia. The second study was conducted for 16 months in one private institution, and its purpose was to estimate the operative characteristics of biological markers of inflammation and clotting as diagnostic tests for sepsis in patients admitted to the emergency room with suspected infection. Both studies were developed from 2007 to 2009. Furthermore, there was a prior research published on the same subpopulations [15]. Both protocols were approved by the ethical committees of the participant institutions. In EPISEPSIS, patients were considered eligible if they were >18 years, had a probable or confirmed diagnosis of infection according to medical records or had changes in temperature (>38 or <36 °C) or hypotension without a specific cause. Furthermore, as definitive inclusion criterion, patients must have had an infection that fulfilled standard Centers for Disease Control and Prevention definitions [16]. In DISEPSIS were included patients hospitalized at the ER within 24 h before admission to the study, aged 18 years or older and with at least one of the following causes as the main admission diagnosis to the hospital: (a) any kind of infectious disease (confirmed or suspected), (b) fever of unknown origin, (c) delirium or any kind of encephalopathy of unknown origin or (d) acute hypotension not explained by hemorrhage, myocardial infarction, stroke or heart failure.

Data collection

One or two nurses were trained depending on the number of beds in each hospital. They followed a training protocol that included 2-day work sessions, and a 3-month pilot study was conducted prior the beginning of the recruitment. In each hospital, there was also a co-researcher physician who was in charge of overseeing data accuracy and consistency, as well as verifying each patient's diagnostic. In addition, each case report form was assessed and revised weekly using a double entry form at Universidad de Antioquia data control center, and any incoherence, inaccuracy or data missing implied returning the specific form to the co-researcher in charge for corrections the following week. Also, one of the main co-researchers conducted an audit in each hospital during the first month of the study.

The severity of an illness was determined using the APACHE II (Acute Physiology and Chronic Health Evaluation II) score [17], and the extent of any organ dysfunction was measured using the SOFA (Sequential Organ Failure Assessment) score [18]. Both scales were applied within the first 24 h after a patient had been included in the respective study. In addition, heart rate, respiratory rate, systolic blood pressure, temperature and Glasgow Coma Scale were collected immediately after admission to the ER and daily, early in the morning during the first week of hospital stay. Furthermore, during the first week and depending on each attending physician in charge of the patient, kidney, respiratory and hematological functions were evaluated by serum creatinine, the ratio PaO_2/FiO_2 and platelet count, respectively.

Measurements and study outcomes

The primary outcomes were changes in heart rate, respiratory rate, systolic blood pressure, temperature, Glasgow Coma Scale, creatinine, PaO_2/FiO_2 and platelets daily during the first week. Twenty-eight-day vital status was determined using outpatient monitoring or calling patients discharged from the hospital before that date.

Statistical analysis

Descriptive statistics is presented using means or medians and their respective dispersion measures, in accordance with the distribution of the variables. To compare proportions, a Chi-square test or a Fisher's exact test was used according to the expected cell values, and to compare continuous variables, a Student's *t* test or a Mann–Whitney test in accordance with the type of data and their distribution was used. For more than two groups with continuous variables, ANOVA or Kruskal–Wallis test, according to data distribution, was used. A P value <0.05 was

considered statistically significant. The analyses of trends during the first week of the clinical and laboratory variables were conducted based on age under or over 65 years old and vital status up to 28 days. Values including heart rate, respiratory rate, systolic blood pressure, temperature, Glasgow Coma Scale, creatinine, PaO_2/FiO_2 and platelets were considered suitable indicators of the clinical response to infection [3].

The rate of change of these variables during the first week, in accordance with age and vital status groups, was estimated using a longitudinal data analysis with a general estimating equation (GEE) method [19]. Using this method, the correction of the dependence within observations (that is, repeated measurements of a variable of the same individual) is made assuming a correlation structure between those measurements. Thus, a normal distribution and an interchangeable correlation structure were assumed, as well as a robust variance estimator (Huber–White) for the estimation [20]. The model estimated variable changes for every day of evolution during the first week in the following groups: alive on day 28 <65 years of age, alive on day 28 ≥65 years of age, dead on day 28 <65 years of age and dead on day 28 ≥65 years of age. The first group was considered the reference group. All statistical analyses were conducted using STATA (version 12.0; StataCorp, College Station, TX 77845, USA).

Results

The two studies included a total of 3486 patients. Eight hundred thirty-five individuals were excluded from the EPISEPSIS cohort because they had nosocomial infections, 40 patients who were admitted directly to the ICU were excluded from the DISEPSIS cohort, and 81, who were enrolled in the study with a different criterion from a suspicion of infection, were also excluded. In total, 2611 patients' data were analyzed: 1846 belonged to the *EPISEPSIS* and 765 to the *DISEPSIS* studies. In both cohorts, when they were characterized per age: groups ≥65 and <65 years of age, significant differences were observed in some comorbidities, APACHE II and SOFA scores, as well as in-hospital and 28-day death rate. In contrast, no differences were found in hospital stay, presence of shock and being admitted to the ICU (Table 1). Since admission, it was evident that patients older than 65 years who died, compared to younger who also died, had less disturbances in heart rate, mean blood pressure, temperature, creatinine and platelets (Table 2).

The general behavior of most clinical and laboratory variables during the first week suggests more dysfunctional responses in subjects under 65 years of age who died 28 days after being hospitalized. From the first day, individuals less than 65 years of age who died seemed to present higher heart rate and temperature values, as well as lower systolic blood pressure and Glasgow Coma Scale values, compared to all the other groups (Fig. 1). The same trend in this group of patients toward greater deterioration during the first week was perceived considering the creatinine values, platelet count and oxygen blood pressure/fraction of inspired oxygen ratio (Fig. 2).

Specifically, compared with patients under 65 years of age alive on day 28 in the EPISEPSIS cohort, the deceased with the same age had an average heart rate of 12.5 beats per minute per day higher during the first week (95% CI 9.3; 15.6). In the same period of time, compared with the same reference group, patients 65 or older who died barely had an average of 5.7 beats per minute more per day (95% CI 3.4; 8.1); instead, the survivors with the same age had an average of 1.6 beats per minute less per day (95% CI −2.8; −0.4). In the DISEPSIS cohort, a similar behavior was observed in the deceased for both age groups (<65 years of age = +20 beats per minute, 95% CI 15.5; 24.7 and ≥65 years of age = +12.9 beats per minute, 95% CI 7.6; 18.7), and there was a non-significant trend toward a heart rate increase in patients 65 or older who survived on day 28 (+0.07 beats per minute, 95% CI −2.1; 2.2) (Table 3). Respiratory rate had significant increases only in patients 65 or older of the EPISEPSIS cohort, independent of the final vital status, and the systolic blood pressure on the first week showed a clear decrease in death patients under 65 years of age in both cohorts (EPISEPSIS—5.2 mmHg, 95% CI −8.17; −2.23 and DISEPSIS—8.5 mmHg, 95% CI −13.4; −3.5), while patients 65 or older with this same outcome showed a nonsignificant increase (+1.6 mmHg, 95% CI −1.3; 4.6 and +0.1, 95% CI −6.4; 6.7, respectively). Temperature increased significantly daily, in comparison with survivors under 65, in the deceased under 65 years of age of both cohorts (+0.2 °C, 95% CI 0.1; 0.4 and +0.5 °C, 95% CI 0.1; 0.8, respectively), but it showed a nonsignificant decreases in the dead 65 years of age or older (Table 3). Platelet values also had greater deterioration in the deceased under 65 compared to patients 65 years of age or older in both cohorts (−67.672 cells/ml, 95% CI −97.613;−37.730 and −90.467, 95% CI −143.862; −37.071, respectively) even though this trend was inverted starting on day 4 for the EPISEPSIS cohort (Fig. 2. Deceased 65 years of age or older: −68.526 cells/ml, 95% CI −100.911; −36.141) and it was not significant in this same group in the DISEPSIS cohort (–5.630, 95% CI −43.014; 31.754) (Table 4.).

Table 1 Baseline characteristics of the study populations

Variables	EPISEPSIS cohort $n = 1846$			DISEPSIS cohort $n = 765$		
	<65 years of age ($n = 1115$, 60%)	≥65 years of age ($n = 731$, 40%)	*P* values	<65 years of age ($n = 526$, 69%)	≥65 years of age ($n = 239$, 31%)	*P* values
Age (years), mean ± SD	42 ± 14	77 ± 8	<0.001	41 ± 14	75 ± 7	<0.001
Female	559 (50.1%)	406 (55.5%)	0.023	262 (49.8%)	126 (52.7%)	0.456
HIV/AIDS	67 (6%)	2 (0.3%)	<0.001	19 (3.6%)	0	0.002
Trauma or surgery in the last 30 days	230 (20.6%)	90 (12.3%)	<0.001	39 (7.4%)	14 (5.9%)	0.432
CHF	66 (5.9%)	95 (13%)	<0.001	8 (1.5%)	16 (6.7%)	<0.001
Transplanted patient	35 (3.1%)	3 (0.4%)	<0.001	45 (8.6%)	4 (1.7%)	<0.001
Cirrhosis	13 (1.2%)	11 (1.5%)	0.530	7 (1.3%)	1 (0.4%)	0.446
Use of steroids or chemotherapy	90 (8.1%)	44 (6.0%)	0.096	61 (12%)	9 (3.8%)	<0.001
Drug addiction/alcoholism	54 (4.8%)	9 (1.2%)	<0.001	5 (0.9%)	0	0.332
COPD	61 (5.5%)	129 (17.6%)	<0.001	25 (4.7%)	69 (28.9%)	<0.001
CKD and/or dialysis	101 (9.1%)	85 (11.6%)	0.073	64 (12%)	24 (10%)	0.393
DM	118 (10.6%)	179 (24.5%)	<0.001	75 (14.3%)	71 (29.7%)	<0.001
History of cancer in the last year	99 (8.9%)	63 (8.6%)	0.847	40 (7.6%)	26 (10.9%)	0.135
APACHE II scoring system, median (IQR)	8 (4–14)	14 (10–19)	<0.001	8 (4–13)	13 (9–16%)	<0.001
SOFA scoring system, median (IQR)	2 (1–5)	3 (2–6)	<0.001	2 (1–4)	3 (2–4%)	0.008
Hospital stay (days), median (IQR)	7 (4–13)	8 (4–14)	0.506	8 (5–16)	10 (7–18)	0.4643
Shock	112 (10%)	72 (10%)	0.891	11 (2%)	4 (2%)	0.699
Admitted to the ICU	86 (7.7%)	79 (10.8%)	0.055	48 (9.1%)	18 (7.5%)	0.467
In-hospital death rate	121 (10.9%)	155 (21.3%)	<0.001	43 (8.2%)	36 (15.1%)	0.004
28-Day death rate	132 (11.9%)	171 (23.4%)	<0.001	48 (9.2%)	43 (18.0%)	<0.001

HIV/AIDS human immunodeficiency virus/acquired immunodeficiency syndrome, *CHF* chronic heart failure, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *DM* diabetes mellitus, *ICU* intensive care unit

Discussion

It is estimated that from 1998 to 2025, the world population over 65 years of age will be more than double, while the population under 15 shall only increase 6% [21]. Thus, the study and management of the disease in this population group is one of the great challenges in medicine in the twenty-first century. Infectious diseases, which are very common in the elderly and related to the worst prognosis, are of special importance [12, 22]. Our study shows that patients over 65 hospitalized for infection and who died on day 28 had a lower expression of cardiovascular dysfunction in the first week of hospitalization. This decrease in cardiovascular response is demonstrated by a lower heart rate increase and a nonsignificant increase in systolic blood pressure, compared to the same measurements, in living or dead patients under 65 during the first week of hospital stay. In addition, the elderly who died were unable to increase their body temperature significantly during the first week of hospitalization, and also they showed a trend to a lower clinical expression of deterioration in the first week on the Glasgow Coma Scale and in the platelet count.

Churpek et al. [10] studied vital signs of 422 hospitalized patients with witnessed cardiac arrest. During the 4 h immediately before the arrest, patients over 65 ($n = 273$) had a lower heart rate average (88 vs. 99 beats/min; $P < 0.001$) and diastolic blood pressure (60 vs. 66 mmHg; $P = 0.007$) than people under 65 ($n = 149$). It had been suggested, based on an experimental model on healthy subjects with increasing doses of adrenergic agonists, that normal aging is related to a decrease in both the left ventricular filling reserve and the inotropic response, but without a decrease in chronotropic response [23]. However, we did not find studies which evaluated changes in the cardiovascular response to sepsis of the elderly population [24]. From a molecular point of view, this lesser

Table 2 Vital signs and organ dysfunction measurements at admission to the ER

Variables	EPISEPSIS cohort $n = 1846$					DISEPSIS cohort $n = 765$				
	<65 years of age $n = 1115$		≥65 years of age $n = 731$		*P* values	<65 years of age $n = 526$		≥65 years of age $n = 239$		*P* values
	Alive ($n = 978$, 88%)	Dead ($n = 132$, 12%)	Alive ($n = 559$, 77%)	Dead ($n = 171$, 23%)		Alive ($n = 474$, 91%)	Dead ($n = 48$, 9%)	Alive ($n = 195$, 82%)	Dead ($n = 43$, 18%)	
Heart rate (beats/min)	92 ± 20	102 ± 25	90 ± 19	95 ± 22	<0.001	100 ± 21	108 ± 22	96 ± 19	96 ± 19	<0.001
Respiratory rate (breaths/min)	21 ± 6	22 ± 8	22 ± 6	23 ± 7	0.002	22 ± 7	27 ± 9	22 ± 6	25 ± 7	<0.001
Glasgow Coma Scale	15 (15–15)	15 (7–15)	15 (15–15)	14 (9–15)	<0.001	15 (15–15)	15 (15–15)	15 (15–15)	15 (13–15)	<0.001
Mean blood pressure (mm Hg)	85 ± 15	77 ± 18	88 ± 17	83 ± 18	<0.001	88 ± 19	81 ± 18	91 ± 19	85 ± 15	0.006
Creatinine (mg/dL)	1.5 ± 1.9	2.0 ± 2.7	1.5 ± 1.2	1.8 ± 1.7	0.014	1.8 ± 2.5	2.1 ± 2.2	1.7 ± 1.7	1.7 ± 1.4	0.784
Temperature (°C)	37.2 ± 1.1	37.2 ± 1.4	37.2 ± 1.1	36.8 ± 1.2	<0.001	37.5 ± 1.1	37.3 ± 1.3	37.3 ± 1.1	36.9 ± 0.8	<0.001
Platelets (cells/mL)	301,990 ± 163,314	245,191 ± 173,219	281,012 ± 143,564	266,312 ± 161,343	<0.001	303,951 ± 144,439	225,638 ± 158,088	304,072 ± 134,439	257,786 ± 151,320	0.001
PaO_2/FiO_2	317 ± 107	240 ± 114	300 ± 106	241 ± 107	<0.001	322 ± 106	238 ± 123	290 ± 91	252 ± 98	<0.001

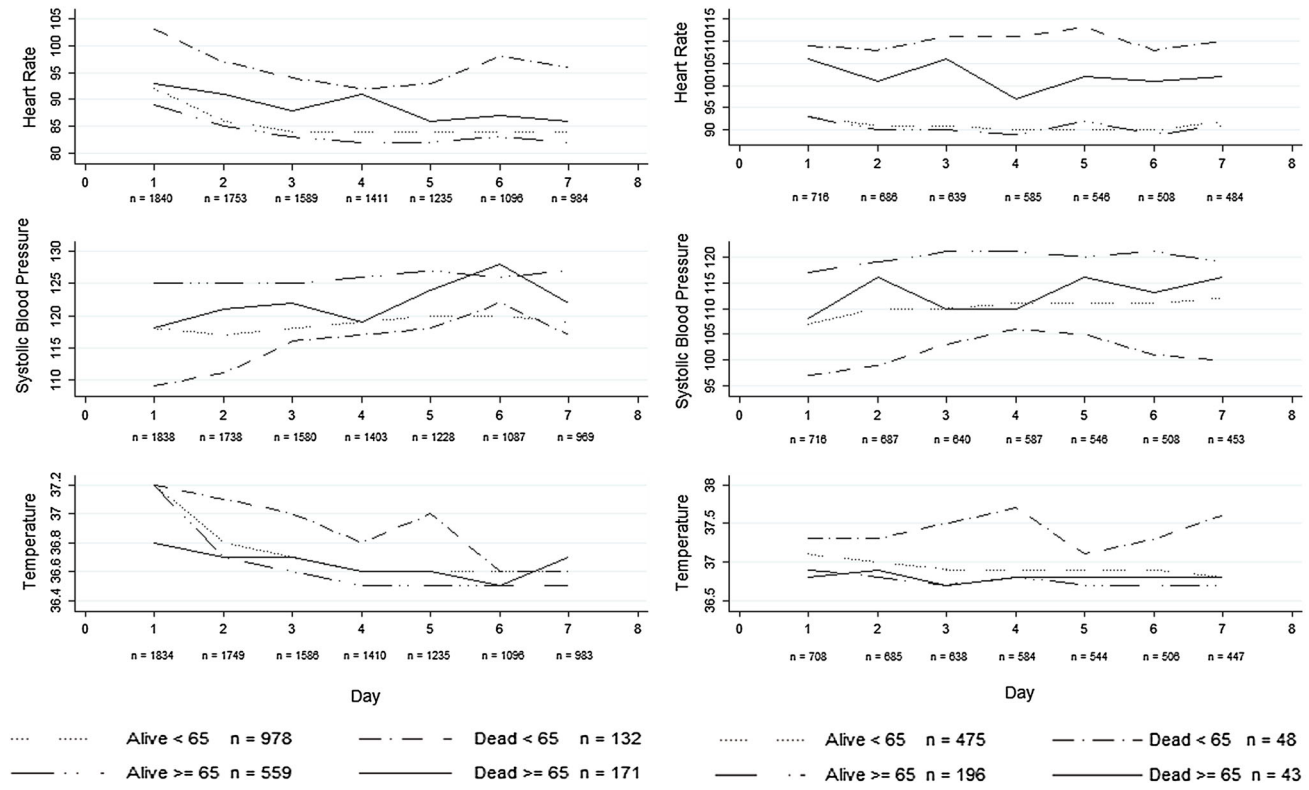

Fig. 1 Average daily values of vital signs by age and vital status (left EPISEPSIS, right DISEPSIS)

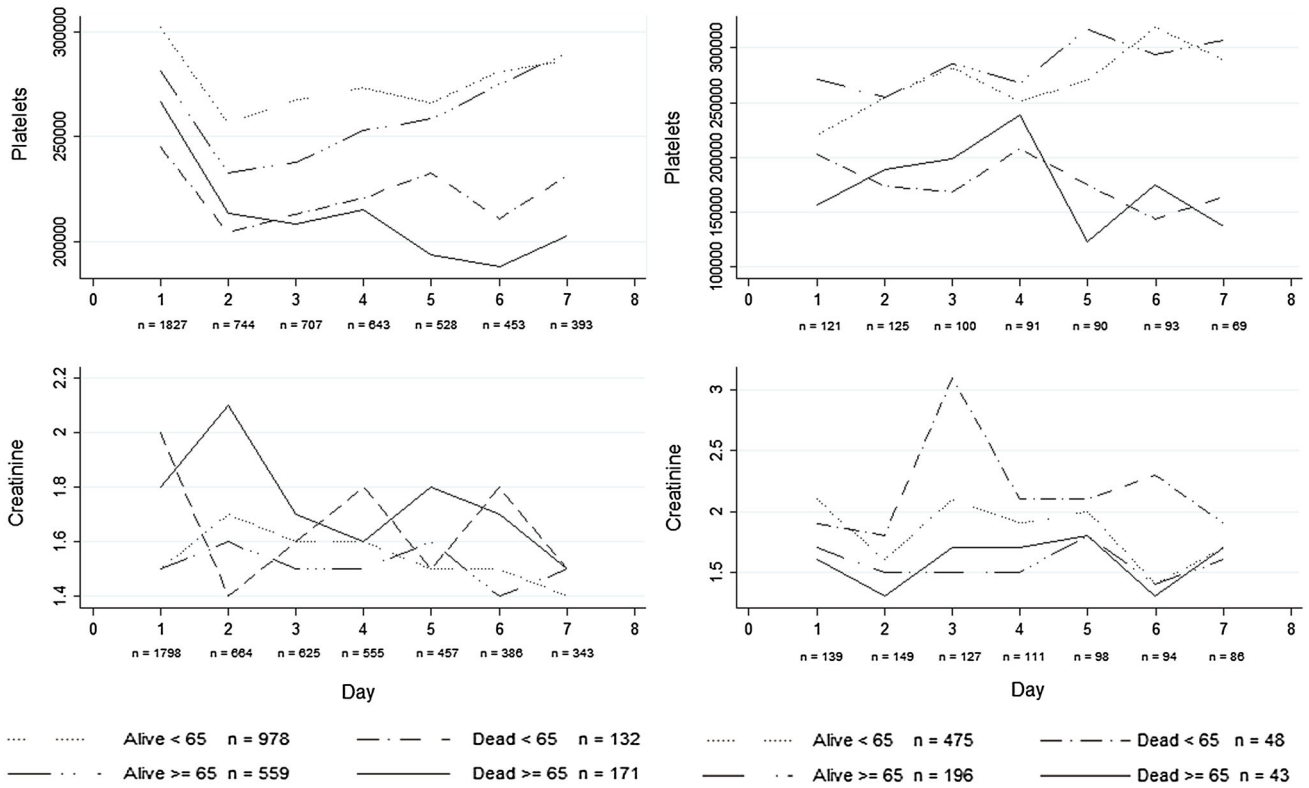

Fig. 2 Average daily values of platelet count and creatinine by age and vital status (left EPISEPSIS, right DISEPSIS)

Table 3 Average rate of daily change in clinical variables by age and vital status

Covariates	EPISEPSIS			DISEPSIS		
	Expected value	95% CI	*P* values	Expected value	95% CI	*P* values
Heart rate (beats/min)						
<65 years of age—alive	86	Reference		90	Reference	
<65 years of age—dead	+12.5	9.3 to 15.6	<0.001	+20	15.5 to 24.7	<0.001
≥65 years of age—dead	+5.7	3.5 to 8.1	<0.001	+12.9	7.6 to 18.7	<0.001
≥ 65 years of age—alive	−1.6	−2.8 to −0.4	0.010	+0.07	−2.1 to 2.2	0.949
Respiratory rate (breaths/min)						
<65 years of age—alive	20	Reference		22	Reference	
<65 years of age—dead	+0.8	−0.2 to 1.7	0.103	+2.2	−0.3 to 4.8	0.078
≥65 years of age—dead	+1.9	1.1 to 2.7	<0.001	+2.8	−1.0 to 6.6	0.146
≥65 years of age—alive	+0.6	0.2 to 1.0	0.001	+0.7	−0.9 to 2.3	0.393
Glasgow Coma Scale						
<65 years of age—alive	14	Reference				
<65 years of age—dead	−3.6	−4.4 to −2.8	<0.001			
≥65 years of age—dead	−3.2	−3.8 to 2.6	<0.001	–	–	–
≥65 years of age—alive	−0.3	−0.5 to −0.1	0.003			
Systolic blood pressure (mmHg)						
<65 years of age—alive	118	Reference		110	Reference	
<65 years of age—dead	−5.2	−8.2 to −2.2	0.001	−8.5	−13.5 to −3.5	0.001
≥65 years of age—dead	+1.6	−1.3 to 4.6	0.278	+0.1	−6.5 to 6.7	0.971
≥65 years of age—alive	+7.4	5.7 to 9.1	0.000	+9.0	6.2 to 11.9	<0.001
Temperature (°C)						
<65 years of age—alive	36.8	Reference		36.9	Reference	
<65 years of age—dead	+0.2	0.09 to 0.4	0.002	+0.5	0.1 to 0.8	0.005
≥65 years of age—dead	−0.06	−0.2 to 0.05	0.287	−0.1	−0.3 to 0.04	0.153
≥65 years of age—alive	−0.08	−0.1 to −0.03	0.002	−0.1	−0.2 to −0.05	0.002

hypotensive response in elderly patients could be explained by an endothelial aging process, which leads to an increase in oxidative stress with a nitric oxide decrease and an increase in the production of elastases and metalloproteinases in smooth vascular muscle [25, 26]. This explains why elderly patients have more rigidness on their arterial walls [27, 28], with an accelerated process of atherosclerosis and hypertension [29] that decrease arterial wall elasticity and leads to higher values of blood pressure [30].

The febrile response in the elderly has been characterized as deficient even in patients with bacteremia, who seems to have a greater risk of death [24, 31]. It has been suggested that there may not be any fever in 20–30% of the elderly with a severe infection [32]. A recent study on 175 patients admitted to the ICU with sepsis showed that in patients over 65 the independent prognostic factors for mortality were SAPS II score and temperature, the last one with an odds ratio for each Celsius degree increase of 0.51 (95% CI 0.31; 0.85) [33]. In fact, even in standard physiological conditions, an elderly adult's average temperature seems to be lower than a young adult's. Gomolin et al. [34] studied the average temperature in the elderly over 65 at different times during the day, finding a range from 36.3 to 36.5 °C without any apparent variations between day and night but with a constant relationship between higher age and lower temperature.

Platelet values are considered a reproducible marker of hematologic dysfunction in patients with sepsis. Zakynthinos et al. [35] demonstrated that patients with acute sepsis and septic shock, compared to sepsis patients without organ dysfunction, significantly increased circulating thrombopoietin levels and decreased platelet counts with high serial measurement of interleukin 6 (IL-6) peaks constantly preceding those changes. Recently, Rondina et al. [36] evaluated the platelet–monocyte aggregation (PMA) increase as a marker for inflammation and death risk related to age in severe sepsis. Comparing 28 patients with severe sepsis or septic shock over 65 years to 85 patients under 65 in the same condition, while PMA values were lower in the first group, the expression of PMA higher

Table 4 Average rate of daily change in laboratory variables by age and vital status

Covariates	EPISEPSIS			DISEPSIS		
	Expected value	95% CI	*P* values	Expected value	95% CI	*P* values
Creatinine (mg/dL)						
<65 years of age—alive	1.5	Reference		1.8	Reference	
<65 years of age—dead	+0.4	−0.01 to 0.8	0.057	+0.6	−0.07 to 1.2	0.081
≥65 years of age—dead	+0.3	0.05 to 0.5	0.016	−0.3	−0.8 to 1.2	0.199
≥65 years of age—alive	−0.05	−0.2 to 0.1	0.501	−0.3	−0.6 to 0.1	0.182
Platelets (cells/mL)						
<65 years of age—alive	301,947	Reference		299,791	Reference	
<65 years of age—dead	−67,672	−97,613 to −37,730	<0.001	−90,467	−143,862 to −37,071	0.001
≥65 years of age—dead	−54,021	−77,818 to −30,223	<0.001	−5630	−43,014 to 31,754	0.768
≥65 years of age—alive	−24,237	−39,308 to −9166	0.002	−123,769	−177,454 to −70,085	<0.001
PaO_2/FiO_2						
< 65 years of age—alive	315	Reference		225	Reference	
< 65 years of age—dead	−80.3	−98.4 to −62.2	<0.001	−35.9	−83.9 to 12.1	0.143
≥ 65 years of age—dead	−74.3	−90.2 to −58.3	<0.001	−47.5	−85.0 to −9.9	0.013
≥ 65 years of age—alive	−17.7	−28.1 to −7.4	0.001	18.9	−18.7 to 56.5	0.326

than 8.4% was related to a death risk almost 6 times higher (HR 5.6; 95% CI 0.6; 49.6) just in patients over 65 years of age. Instead, in patients under 65, increased PMA values did not represent any type of risk (HR 0.9; 95% CI 0.2; 2.7) [36]. Although we did not find any study similar to ours regarding platelet counts, the above results could suggest that in the elderly with sepsis, the lower IL-6 production and lower platelet activation may partially contribute to the presence of a relatively higher number of circulating platelets in the blood.

The different clinical and laboratory manifestations present in sepsis patients are due, among other factors, to each individual's natural immune response and to numerous inflammatory ways unleashed by the presence of different antigens in the body [11, 37]. In elderly patients, who were defined in our study as an individual 65 or older, the phenomenon of *immunosenescence* occurs. It is a state of immune system dysfunction defined as lower capacity for immunological responses, and this grants the elderly a different view from a clinical and physiopathological point of view [11, 13, 38]. Alterations in innate and adaptive immune responses have been identified in this process [38]. A decrease in the phagocytic ability of neutrophils and macrophages has been described, as well as a decrease in interleukin production (tumor necrosis factor, interferon gamma and interleukin 6) and in the expression of the class II major histocompatibility complex (MHC) in these cells [13, 39]. In view of the decrease in the frequency and functionality of several immune cells, it is expected that this response will be delayed or decreased with the obvious clinical impact. Delayed sepsis identification and diagnosis leads to a late start of appropriate treatment, favoring organ dysfunction and potentially fatal outcomes. Thus, it is of the utmost importance to characterize elderly patients' clinical and laboratory responses when they undergo the physiopathological stress of an infection and sepsis.

Our study has several limitations. It is a secondary analysis of two prospective cohort studies, and it was not designed with the objective of finding vital signs differences in populations from different age groups. Eligible patients were detected in the first 24 h after being admitted to the ER, but most likely their infections had different evolution times before study entry. We do not have data regarding the treatment they received, which could have modified vital signs and laboratory parameters during the first days of monitoring. Finally, the population had significant differences in some comorbidities and in their baseline physiological status, in accordance with the APACHE II and SOFA scores, so it is not possible to establish a sequential and causal relation between clinical manifestations, severity, treatment and final prognostic.

Our findings allow us to conclude that the population of 65 years of age or older presents a systemic response to infection different from that observed in young adult population. This attenuated response was evidenced by less vital signs alteration, including systolic blood pressure, heart rate and temperature, and in laboratory parameters as platelet counts. The above obligates us to have special considerations for the diagnosis and monitoring of elderly patients with sepsis because their clinical manifestations

are different. Thus, traditional vital signs and laboratory alterations that have been commonly pointed out to consider sepsis in an adult population must have differences in this age group [6]. Additional studies should be conducted to clearly establish which variables allow an early identification of those elderly patients with severe infections at high death risk.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The procedures followed were in accordance with the ethical standards of the responsible committee on human research (institutional and national).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent As the studies were observational and we did not take data directly from the patients, the ethical committees approved us a verbal informed consent.

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