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ORIGINAL RESEARCH

Sex-related mortality differences in young adult septic shock patients

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Abstract

Septic shock survival rate and host immune response are intimately interlaced. In the last years, biological and pre-clinical studies demonstrated sex-specific differences in the immune response to infection. In the hypothesis that survival rate is related to the hormonal framework, the aim of the present study was to observe sex-specific differences in 28-day mortality rate between women of childbearing potential and same-age men. This multicenter study was conducted in six Italian intensive care units (ICUs). We enrolled consecutive patients $\leq$ 55 years old admitted to the Intensive Care Unit from January 2011 to January 2020, who were diagnosed with septic shock at the time of ICU admission or during the ICU stay. We gathered baseline characteristics and outcomes. The primary outcome was 28-day mortality; secondary outcomes included ICU mortality, in-hospital mortality and length of stay in the ICU and in the hospital. Moreover, data from >55 years old patients were collected and analyzed. We enrolled 361 young patients with septic shock: 215 were males (60%) and 146 females (40%). While baseline and ICU characteristics were similar between the two groups, males had a higher 28-day mortality rate (39.5% *vs.* 29%, $p = 0.035$), ICU mortality rate (49% *vs.* 38%, $p = 0.040$) and hospital mortality rate (61% *vs.* 50%, $p = 0.040$) as compared to females. Findings were confirmed in patients with septic shock at ICU admission. Young adult females developed septic shock less frequently than young males, displaying a reduced mortality rate as compared to that of their same-age male counterpart. These findings may stimulate future research and therapies.

Keywords

Sex; Gender; Septic shock; Intensive Care Unit; Mortality

1. Introduction

Septic shock has a high prevalence worldwide with a mortality rate of around 38% [1]. Approximately 10% of Intensive Care Unit (ICU) patients are diagnosed with septic shock at the time of admission and an additional 8% develop it during the ICU stay [2].

Mortality predictors and prognostic factors have been studied in order to improve patient management and sepsis survival rate [3, 4]. In the last years, innovation in molecular biology and pre-clinical studies provided keen insights into the pathophysiology of sepsis, allowing for recognition of the central role of immunity in septic shock-related organ failure [5].

Sex-differences in immune response are well known and were found to be closely related to the different hormonal and genetic framework of women of childbearing potential

and same-age men [6]. While the connection between the hormonal profile and the host response to infection was well described by preclinical data, evidence from clinical observations is still lacking [7].

Septic shock is more prevalent in males [2]. Previous studies analyzed the affected population without considering the age variable, and showed no sex related differences in survival rates [8].

Our hypothesis was that septic shock survival rate is influenced by a hormone-driven diversity in the immune response of women of childbearing age as compared to men of the same age. The aim of the present study was to focus on sex-specific differences in 28-day mortality of young adult patients with septic shock admitted to the ICU.

2. Methods

2.1 Patient selection

The study was conducted in six Italian ICUs. Ethical committee approval was not required according to the Italian law since data were retrospectively collected and completely anonymized. All consecutive patients admitted to ICU from 1st January 2011 to 1st January 2020 were screened for enrollment.

Septic shock was defined and treated according to the latest international guidelines available: sepsis-1 criteria [9] were employed to identify septic shock patients admitted to the ICU before January 2013; sepsis-2 criteria [10] were used for definition of septic shock from January 2013 to February 2016; sepsis-3 criteria [5] were applied to recognize patients admitted to the ICU for septic shock after February 2016.

Inclusion criteria were: age 18–55 years old; ICU admission; diagnosis of septic shock (either at the time of ICU admission or during the ICU stay). Patients younger than 18 years old were excluded from the study.

Baseline characteristics, comorbidities, hospitalization data, Glasgow coma scale score, Simplified Acute Physiology Score (SAPS) II score and Sequential Organ Failure Assessment (SOFA) score, infection indices and administered therapies were collected for every patient during the ICU stay.

To assess the influence of sex-related immune status on outcomes, data from patients >55 years were also collected. We defined as "young" those patients between 18–55 years old [11] and "elderly" those older than 55. This cut-off was chosen according to gynecological and endocrinological changes between the pre- and post-menopausal periods [12, 13].

The primary outcome of the study was the sex-related difference in 28-day mortality rates in young patients. Secondary outcomes included ICU and hospital mortality, length of stay in the ICU and length of stay in the hospital.

Analyses were repeated in elderly patients and in the overall population.

2.2 Statistical analysis

Qualitative variables were expressed as numbers and percentages; quantitative variables were reported as median and interquartile range. Chi-square and Fisher exact tests were used to compare categorical variables. To compare continuous variables between groups we employed nonparametric tests. Odds ratio and 95% confidence interval were used and a p value of 0.05 or lower was considered as statistically significant. Statistical analysis was performed using the software STATA v16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA) and SPSS v20 (IBM Corp., Armonk, NY, United States).

3. Results

A total of 1849 consecutive patients with septic shock were managed in six ICUs during the aforementioned study period. Young patients ($\leq$ 55 years old) were 361 (19.5%) of which males were 215 (60%) and females 146 (40%).

According to baseline characteristics (Table 1) males were older and displayed a higher rate of hepatic failure, while females were more prone to the development of autoimmune disorders and more frequently required dialytic treatment. No differences were found in SOFA and SAPS II scores, as well as microbiological features, source of infection and baseline severity of sepsis between males and females (Table 2). Moreover, the neurological status and need for invasive treatments, during the ICU stay, were similar between groups (**Supplemental Table 1**). Mortality at the 28-day follow up of young females and males was, respectively, 85/215 (39.5%) and 42/146 (29%) (p = 0.035) (Fig. 1 A). Magnitude and direction of findings were confirmed after adjusting for age, however statistical significance was lost (p = 0.098) probably because of the limited sample size. Findings were confirmed for ICU mortality rate (49% *vs.* 38%, p = 0.040 which became p = 0.066 after further adjusting for age) and in-hospital mortality rate (61% *vs.* 50%, p = 0.040 which became p = 0.085 after further adjusting for age) (Table 3). ICU and hospital length of stay in the overall population and in survivors were similar between groups (Table 3).

Subgroup analyses on patients with septic shock at the time of ICU admission confirmed an increased 28-mortality among young males, as compared to young females (22/50 males (44%) *vs.* 10/41 women died (24%), p = 0.045). Findings were similar for ICU mortality (50% *vs.* 29%, p = 0.045) and in-hospital mortality (60%, 34%, p = 0.01) (Table 4).

When analyzing outcomes in post-menopausal females and same-age males (>55 years old), an opposite trend was observed (e.g. 28-day mortality in males *vs.* females was 338/901 (37.5%) *vs.* 251/587 (42.8%), respectively; p = 0.04) (Table 3; Fig. 1 B).

No differences in mortality were noted in the overall population $\geq$ 18 years old (Table 3). The analysis on patient mortality according to age decades yielded a cut off of around 55 years as a "favoring females" and "favoring males" factor (Table 5).

4. Discussion

This multicenter study confirmed that septic shock is more frequent in males than in females and found higher survival rates among women of childbearing potential, when compared to same-age men. In the general population no sex-related differences in mortality were reported, because the overall impact of women of childbearing potential on epidemiological

TABLE 1. Baseline characteristics of patients 18–55 years old.

	Overall (n = 361)	Males (n = 215)	Females (n = 146)	*p* value
Age, years	47 (40–51)	48 (43–52)	45 (38–51)	0.017
BMI	24.9 (22–29.3)	25.2 (22.5–27.8)	24.4 (20.8–32.9)	0.49
Comorbidities	222 (61.5)	139 (64.7)	83 (56.8)	0.13
Lung disease	30 (8.3)	20 (9.3)	10 (6.8)	0.4
Arterial hypertension	27 (13.6)	15 (12.3)	12 (15.6)	0.5
AMI	11 (5.5)	9 (7.4)	2 (2.6)	0.4
Heart Failure	13 (3.6)	6 (2.8)	7 (4.8)	0.15
DM	40 (11.1)	24 (11.2)	16 (11)	0.95
Stroke	8 (4)	4 (3.3)	4 (5.2)	0.5
Kidney Failure	38 (10.5)	22 (10.2)	16 (11)	0.82
Hepatic Failure	81 (22.5)	58 (27.1)	23 (15.8)	0.01
Malignancy	57 (15.8)	35 (16.3)	22 (15.1)	0.75
Vascular disease	13 (6.5)	6 (4.9)	7 (9.1)	0.24
Immunodeficiency	41 (19.2)	24 (11.1)	17 (11.6)	0.69
AIDS	9 (4.9)	8 (3)	1 (0.6)	0.08
Paraplegia/neuromuscular disease	5 (2.5)	2 (1.6)	3 (3.9)	0.32
Autoimmune disorders	12 (6)	3 (2.5)	9 (11.7)	0.01
Dialysis	10 (5.4)	3 (2.6)	7 (9.9)	0.03
Type of admission				
Medical Ward	209 (57.9)	135 (62.8)	74 (51)	0.055
Surgical Ward	67 (18.5)	30 (14)	37 (25)	
ED	37 (10.2)	23 (10.7)	14 (9.7)	
Transferred from other ICU	9 (2.5)	4 (1.9)	5 (3.4)	
Trauma	14 (3.9)	10 (4.7)	4 (2.7)	0.35
Severity score (at ICU admission)				
GCS	15 (13–15)	15 (14–15)	15 (12–15)	0.089
SOFA	10 (6–13)	10 (6–14)	9 (6–12)	0.13
SAPSII	48 (32–64)	49 (33–64)	44.5 (31–65)	0.9

Data are expressed as median (quartile 25%–75%) or n (%).
Abbreviations: BMI—body mass index; AMI—acute myocardial infarction; DM—diabetes mellitus; AIDS—acquired immune deficiency syndrome; ED—Emergency Department; ICU—Intensive Care Unit; GCS—Glasgow Coma Scale; SOFA—Sequential Organ Failure Assessment; SAPSII—Simplified Acute Physiology Score II.

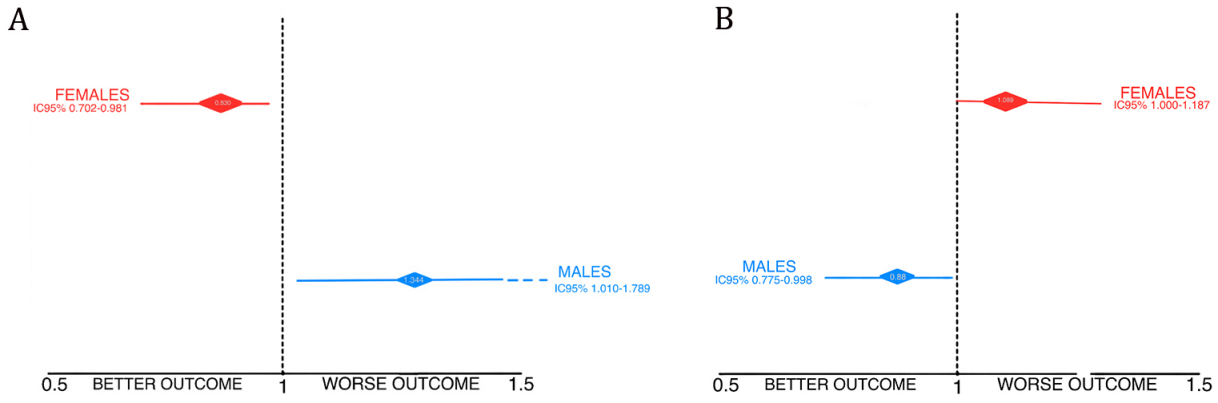

FIGURE 1. 28 day mortality in patients 18–55 years old (panel A) and in patients >55 years old (panel B).

TABLE 2. Microbiological characteristics of patients 18–55 years old.

	Overall (n = 361)	Males (n = 215)	Females (n = 146)	*p* value
Source of infection				0.11
Lungs	130 (36)	83 (38.5)	47 (32)	
Abdomen	71 (19.7)	42 (19.5)	29 (20)	
UTI	6 (1.7)	0	6 (4)	
Skin	7 (1.9)	4 (2)	3 (2)	
CNS	2 (0.5)	1 (0.5)	1 (0.7)	
Bloodstream	52 (14.4)	30 (14)	22 (15)	
Mediastinitis	6 (1.7)	5 (2)	1 (0.7)	
Others	35 (9.7)	18 (5.6)	17 (6.8)	
Characteristics at ICU admission				0.15
No infection	79 (21.9)	44 (25)	35 (24)	
Infection	110 (30.5)	64 (30)	46 (31.5)	
Sepsis	81 (22.4)	57 (27)	24 (16.5)	
Septic shock	91 (25.2)	50 (23)	41 (28)	

Data are expressed as number and percentage n (%).
Abbreviations: UTI—Urinary tract infection; CNS—central nervous system; ICU—Intensive care unit.

TABLE 3. Mortality (of patients 18–55 years old, >55 years old and of the general population) ICU and hospital length of stay.

Classification	Number			*p* value
Young patients (18–55 years)	Overall (n = 361)	Males (n = 215)	Females (n = 146)	
28-days mortality	127 (35.2)	85 (39.5)	42 (28.8)	0.035
ICU mortality	162 (44.9)	106 (49.3)	56 (38.4)	0.04
Hospital mortality	204 (56.5)	131 (60.9)	73 (50)	0.04
Patients >55 years	Overall (n = 1489)	Males (n = 902)	Females (n = 587)	
28-days mortality	589 (39.5)	338 (37.5)	251 (42.8)	0.048
ICU mortality	775 (52)	488 (54.2)	287 (48.9)	0.049
Hospital mortality	894 (60)	535 (59.4)	359 (61.2)	0.49
General population (>18 years)	Overall (n = 1850)	Males (n = 1117)	Females (n = 733)	
28-days mortality	716 (38.7)	423 (37.9)	293 (40)	0.37
ICU mortality	875 (47.3)	519 (46.5)	356 (48.5)	0.38
Hospital mortality	1098 (59.3)	666 (59.7)	432 (58.9)	0.75
ICU length of stay (>18 years)				
Overall, days	8 (3–15)	7 (3–13)	9 (4–16)	0.28
Survivors, days	9 (4–16)	8 (4–16)	9 (4–18)	0.94
Hospital length of stay (>18 years)				
Overall, days	26 (12–46)	25 (11–45)	27 (13–47)	0.78
Survivors, days	31 (20–53)	32 (21–52)	30.5 (16.5–55)	0.36

Data are expressed as median (quartile 25%–75%) or n (%).
Abbreviations: ICU—intensive care unit.

frequency measures was negligible.

Septic shock represents one of the main and unsolved problems of intensive care medicine. International studies involving thousands of male and female patients not sorted by age failed to identify sex-related differences in mortality [3]. In line with previously published data, when the overall

TABLE 4. Mortality rate in patients 18–55 years old admitted with septic shock and in those who developed it during ICU stay.

	Overall (n = 361)	Males (n = 215)	Females (n = 146)	*p* value
Admitted with septic shock				
28-days mortality	32 (35.2)	22 (44)	10 (24.4)	0.045
ICU mortality	37 (40.7)	25 (50)	12 (29.3)	0.045
Hospital mortality	44 (48.3)	30 (60)	14 (34.1)	0.014
Developed septic shock during ICU stay				
28-days mortality	95 (35.2)	63 (38.2)	32 (30.5)	0.19
ICU mortality	125 (46.3)	81 (49)	44 (42)	0.24
Hospital mortality	160 (59.3)	101 (61.2)	59 (56.2)	0.41

Data are expressed as numbers and percentages n (%).
Abbreviations: ICU—intensive care unit.

TABLE 5. Decades analysis.

	Overall (n = 1850)	Males (n = 1117)	Females (n = 733)
28-days mortality			
≤35 years	15 (25.4)	9 (29)	6 (21.4)
36–45 years	19 (20.2)	14 (37.8)	5 (12.5)
46–55 years	80 (38.3)	53 (41)	27 (40.3)
56–65 years	136 (35.1)	86 (35.4)	50 (34.5)
66–75years	210 (38.6)	119 (35.1)	91 (44.4)
>75 years	243 (43.7)	133 (41.7)	110 (46.4)
ICU mortality			
≤35 years	22 (37.3)	12 (38.7)	10 (35.7)
36–45 years	28 (29.8)	17 (46)	11 (27.5)
46–55 years	95 (45.5)	66 (51)	29 (43)
56–65 years	184 (47.4)	118 (48.6)	66 (45.5)
66–75 years	274 (50,4)	158 (46.6)	116 (56.6)
>75 years	255 (45.9)	137 (42.9)	118 (49.8)
Hospital mortality			
≤35 years	29 (49.1)	19 (61.3)	10 (35.7)
36–45 years	39 (41.5)	23 (62.2)	16 (40)
46–55 years	115 (55)	75 (58)	40 (59.7)
56–65 years	215 (55.4)	138 (56.8)	77(53.1)
66–75 years	337 (61.9)	207 (61)	130 (63.4)
>75 years	342 (61.5)	190 (59.6)	152 (64.1)

Data are expressed as median (quartile 25%–quartile 75%) or n (%).
Abbreviations: ICU—intensive care unit.

population was analyzed, we found no differences in septic shock mortality rates between females and males.

In general, males developed septic shock more frequently than females: a high male/female ratio was repeatedly observed in previous reports [14]. Male gender predisposes to severe sepsis and septic shock in all age groups [15]. While sepsis is more common in male children, there is no difference in mortality between males and females in pre-puberal ages [16]. However, to-date sex-related differences in mortality are still unknown [17, 18] and current data are inconclusive. We suggest that previous studies may have shown conflicting findings because the population was not sorted according to the childbearing potential.

Considerable efforts were made to fully understand the pathogenetic pathways underlying the sex-related differences in septic shock outcomes in young adults, including the role of sex per se and its impact on septic shock severity and mortality. Young adult females seldom develop septic shock

and once admitted to the ICU, have lower mortality rates when compared to male patients. Mortality is highly affected by the hormonal milieu and systemic immune response regulation. A large amount of preclinical data supports the role of estrogens in immune regulation after septic shock and tissue damage. Estrogens are known to exert cardio-protective effects [19], improve pulmonary function [20], help preventing renal and hepatic impairment [21], and influence the central nervous system [22].

Pre-clinical and biological plausibility supports sex-difference data. Our clinical data suggest that biological differences may cause a diverse immune response during septic shock, with a protective effect towards females of childbearing potential Female hormones, together with secondary mediators released from tissue damage, modulate the host response lowering microvascular trauma and organ dysfunction or failure.

The strength of our study is to add valuable clinical data to pre-clinical and in-vitro analysis, confirming a correlation between mortality from septic shock and sex We suggest a protective role of female hormones in the host response to septic shock. Our findings may encourage to open up to new therapies and tailored medicine focusing on a tighter modulation of sex-related hormonal status.

The first limitation to our findings is that menopausal age cannot be defined by a cut-off value, but it shows a great inter-individual variability; consequently, it is difficult to universally define age groups. Moreover, data were retrospectively collected and mortality rate changed throughout the study period, thanks to the improved standards of care.

A full understanding of the pathogenesis of septic shock and the central role of hormones (that could be modulated by targeted therapies) is essential to developed new therapeutic strategies and improve the outcome of septic shock patients.

AUTHOR CONTRIBUTIONS

AZ, GL, MG—Ideation of the study and supervision to work; FM, EB, RDS, IC, EM, VPP, GM, GB, AS, GA, DM, MZ, NL, AR, LP, MM, PFB, NP, MBR, OP, GG, GR, MN, SV, MT, EM, MGV, SP —Data collection; FM, GL, MG—Data analysis; FM, RDS, AS, DM, MZ, NL, AR, LP, MG, GL—Manuscript drafting; AZ, EB, RDS, EM, VPP, GM, GB, AS, GA, DM, MZ, AR, LP, MG, GL, MM, PFB, NP, MBR, OP, GG, GR, MN, SV, MT, EM, MGV, SP—Manuscript substantial revision; all authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Landoni Giovanni is serving as one of the Editorial Board members of this journal. We declare that Landoni Giovanni had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to CM.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/15018355953635655 68/attachment/Supplementary%20Table%201.docx.

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