SEPSIS IN THE EMERGENCY ROOM: WHICH ARE THE POOR PROGNOSTIC FACTORS?

Sebastian Dogaru¹, Caius Bogdan Teușdea¹, Florea Purcaru²

¹"Dr. Carol Davila" Central Emergency University Military Hospital, Bucharest, Romania

²University of Medicine and Pharmacy, Craiova, Romania

Corresponding author: Sebastian Dogaru

E-mail: sebidogaru@hotmail.com

Abstract

Background. Understanding the underlying cause of mortality in sepsis has broad implications for both trials design and clinical care. A one-size-fits-it-all treatment without considering underlying comorbidities and particularities of a specific patient may have a huge impact on prognosis.

Materials and methods. We performed a retrospective, single center observational study of patients admitted in Emergency Department taking into account the suspicion of an infection, serious enough to produce a systemic inflammatory response syndrome. Of this population, we selected the septic patient (Sepsis-3 definition) and studied the impact of comorbidities on prognosis.

Results. 125 patients were included. We found that institutionalized patient and respiratory insufficiency were the factors with the biggest impact on prognosis. Close to that, the age was a factor to be taken into account when discussing about prognosis. Other factors as malignancy, diabetes mellitus, cardiac and renal failure were not associated with ominous prognosis, although may have an impact. Two scores (MEDS and NEWS2) and a biomarker were also found to be useful when making a prognosis in such patients.

Conclusions. In this retrospective cohort, the institutionalized patient and patients with with respiratory have poor prognosis, while in other diseases, MEDS, NEWS2 and presepsin were reliable prognostic factors.

Keywords: sepsis, comorbidities, presepsin, MEDS, NEWS2, institutionalized patient, respiratory insufficiency.

Rezumat

Introducere. Înțelegerea cauzei care stă la baza decesului în sepsis are implicații majore atât cu privire la modul de concepere a studiilor clinice, cât și cu privire la modul de acordare a asistenței medicale. Un tratament nediferențiat pentru toți pacienții, care nu ia în considerare comorbiditățile și particularitățile fiecăruia, poate avea un impact uriaș asupra prognosticului.

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Material și metodă. Am realizat un studiu observațional, la nivelul unui singur centru, retrospectiv, cu pacienții care s-au prezentat la Unitatea de Primiri Urgențe, care au avut ca și suspiciune de prezentare o infecție, destul de serioasă astfel încât să producă un sindrom de răspuns inflamator sistemic. Din acest lot de pacienți am selectat pacienții cu sepsis (în conformitate cu definiția Sepsis-3) și am studiat impactul comorbidităților asupra prognosticului.

Rezultate. În studiu au fost incluși 125 de pacienți. Pacienții instituționalizați și insuficiența respiratorie au fost factorii cu impactul cel mai mare asupra prognosticului. Apoi, vârsta a fost un factor de luat în calcul atunci când se discută despre pronostic. Alți factori cum ar fi malignitatea, diabetul zaharat, insuficiența cardiacă și renală nu au fost asociați cu un pronostic infaust, deși aceștia îl pot influența. Două scoruri (MEDS, NEWS2) și un biomarker pot ajuta la estimarea prognosticului la acești pacienți.

Concluzii: În studiul retrospectiv efectuat pe această cohortă, pacienții instituționalizați și cei cu insuficiență respiratorie au avut un prognostic nefavorabil, în timp ce, pentru alte patologii, MEDS, NEWS2 și presepsinul au fost factori prognostici de încredere.

Cuvinte cheie: sepsis, comorbidități, presepsin, MEDS, NEWS2, pacient instituționalizat, insuficiență respiratorie.

Introduction

Sepsis is a common and highly morbid clinical syndrome that affects more than 850 000 patients in the United States each year⁽¹⁾ and is also an important global health problem. It is estimated to affect more than 30 million people worldwide every year, potentially leading to 6 million deaths⁽²⁾. Although hospital survival rates have been improving in the past decade^(3,4), there still much to be done and mortality remain high. Sepsis is still the most common reason for death in

noncardiac intensive care units (ICU)⁽⁵⁾. However, sepsis is only the tip of the iceberg. The normal contact to an infectious agent can lead to a local inflammatory reaction, usually neutralized, but in certain cases this can further develop into a systemic inflammatory reaction syndrome with a possible evolution to sepsis, septic shock and death. All these conditions are only possible stages of evolution and not a must. Depending on not entirely known factors, any of these stages can be reversed and we believe that the multiple comorbidities may have a role.

Although a widespread syndrome, sepsis, a life-threatening organ dysfunction due to a dysregulated host response to infection⁽⁶⁾, is not the only diagnosis, but one of the many of a specific patient. Reporting sepsis without considering the other comorbidities may obscure important heterogeneity as reasons for death among septic patients⁽⁷⁾. Many scores were developed in order to predict the evolution of an infection to this final life-threatening condition. As an additional tool, many biomarkers were studied, but the final conclusions were not drawn.

In the present study, we tried to assess the impact of comorbidities in patients with sepsis and septic shock evaluated in Emergency Room (ER). We also tried to apply different scores, a biomarker, presepsin, in order to assess the outcome.

Material and methods

1. Study population

This was a retrospective, single-center observational cohort study of 125 patients who were diagnosed with systemic inflammatory response syndrome between July 2016 and July 2018 at Emergency Department of “Dr. Carol Davila” Central Military Emergency University Hospital, Bucharest, Romania in order to determine the risk factors of illness and the aetiology of illness. All patients were above 18 years old and have agreed to sign the informed consent. The study was approved by the institutional ethics committee of “Dr. Carol Davila” Central Emergency University Military Hospital, Bucharest, Romania.

2. Developing a tool for reporting impact of comorbidities

Five categories of comorbidities which can have an impact to the future evolution of the

patient were evaluated. These were: the malignancy, diabetes mellitus, heart failure, kidney failure, respiratory failure. We also took into account another possible prognostic factor, the institutionalized patient.

3. Retrospective view

The following information was abstracted from the electronic medical record: age, sex, medical comorbidities, initial laboratory values from the hospital admission, suspected source of infection. Based on these information following scores were calculated: qSOFA⁽⁶⁾, as a diagnose for sepsis, NEWS2 (National Early Warning Score 2)⁽⁸⁾, and MEDS⁽⁹⁾ (Mortality in Emergency Department Sepsis). The clinical data for the patients included in the study were gathered retrospectively from the patient records by the principal investigator (S.D).

Statistical analysis

Descriptive statistics were used to summarize the study population. Categorical variables are presented as counts and percentages. Independent samples test with Levene's test for equality of variances and t-test for equality of means were used. Chi-square test was used for categorical variables. IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

Demographics

There were 125 consecutive patients which were considered to have SIRS (systemic inflammatory response syndrome) and included in the study. From these 30 were diagnosed as having sepsis (Sepsis-3 definition, with 2 or more qSOFA criteria) and 11 were diagnosed as having septic shock.

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The median age was of 70,88 years with standard deviation of 15,74 years; they ranged from 18 to 96 years. Of the total study population, 79 (63,2%) were men. Table 1 provides the demographic data, the calculated scores, selected comorbidities and the site of infection.

The distribution of demographic (sex distribution) and clinical parameters (presence of neoplasia, diabetes, cardiac failure, renal failure and respiratory failure) are shown in Figures 1-6. Further studies can elucidate if male sex is a risk factor for sepsis, septic shock and mortality or it is a bias due to the reduced number of patients included in our study. Even if diabetes mellitus, heart, kidney and pulmonary diseases are very often met, as the patients age increases, multiple comorbidities can complicate the evolution of one specific patient. Also, the biomarker clearance may be influenced by of a particular comorbidity, so a one-fits-all approaches must be avoided.

Impact of clinical laboratory and specific scores on mortality

Clinical, laboratory parameters and specific scores in deceased patients vs survivors are detailed in Table 2. All the scores (qSOFA, MEDS and NEWS2) are significantly increased in deceased patients. Interestingly, the level of potassium was significantly increased in these patients ($4,67 \pm 0,97$ vs $4,15 \pm 0,96$, $p=0.01$).

The mortality rate in patients with comorbidities are presented in Figures 7-11. Respiratory failure was associated with an increased risk for death comparing with patients without respiratory failure (8/20 pts. vs 19/105 pts., $p=0.03$).

The mean age of deceased patients was higher than survivors, but without reaching statistical significance (75.63 ± 14.70 vs 69.59 ± 15.92 , $p=0.07$).

Impact of institutionalized patient on mortality

A special emphasis must be shown in correlation with the institutionalized patient. Although only a small cohort was obtained, the results were somehow surprising. Of the 7 institutionalized patients 5,6% of the cohort, 3 (42,85%) have died of sepsis, from which one (14,28%) died of septic shock. Altogether, 6 of the 7 (85,71%) have died, the other 3 as a cause of multiple comorbidities. Due to the small sample size, the results might have been biased, but further investigations are mandatory because of such a devastating potential prognostic factor.

As seen, 21 out of 118 patients died being brought from home in the ED, while 6 out 7 institutionalized patients have died ($p=0,0001$), so being institutionalized was significantly associated with the risk of death.

Demographics	All patients (N=125)	Sepsis (N=30)	Septic shock (N=11)	Death (N=27)
Age (mean, SD)	70,888 (15,74406)	73,4666 (15,3139)	72,2727 (15,3391)	75,6296 (14,4277)
Sex (%male)	79 (63,2)	23 (29,11)	10 (12,65)	20 (74,07)
Weight (mean, SD)	71,472 (12,6835)	70,7333 (9,2805)	72,2727 (9,3525)	70,5185 (15,8637)
GCS (mean, SD)	14,264 (2,1841)	12,8666 (2,9970)	12,4545 (2,6064)	13,8148 (2,4651)
MEDS (mean, SD)	9,568 (4,3512)	14,0333 (2,9606)	15,8181 (2,5873)	12,9259 (4,2681)
qSOFA (mean, SD)	0,672 (0,9779)	2,2666 (0,4422)	2,5454 (0,4979)	1,1481 (1,1123)
NEWS2 (mean, SD)	4,768 (3,6532)	9,7333 (2,8511)	12 (2,3741)	6,5925 (4,0208)
Selected comorbidities				
Malignancy (%)	35 (28)	10 (28,57)	2 (5,71)	8 (22,85)
DM (%)	27 (21,6)	9 (33,33)	4 (14,81)	6 (22,22)
CF (%)	49 (39,2)	9(18,36)	4 (8,16)	13 (26,53)
Kf (%)	36 (28,8)	7 (19,44)	3 (8,33)	11 (30,55)
Rf (%)	20 (16)	8 (40)	3 (15)	8 (40)
Institutionalized patient (%)	7 (5,6)	3 (42,85)	1 (14,28)	6 (85,71)
Site of infection				
abdominal (%)	26 (20,8)	6 (23,07)	3 (11,53)	8 (30,76)
cutaneous (%)	15 (12)	1 (6,66)	0	3 (20)
endocard (%)	1 (0,83)	0	0	1 (100)
pulmonary (%)	20 (16)	6 (0,3)	2 (10)	5 (25)
kidney (%)	28 (22,4)	11 (39,28)	5 (17,85)	5 (17,85)
unspecified (%)	35 (28)	6 (17,14)	1 (2,85)	5 (14,28)

Table 1. Cohort characteristics, used scores, selected comorbidities and the site of infection

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Score risk, presepsin and comorbidities

Special considerations should be made as such: in institutionalized patients 2 significant prognostic factors for mortality were found: presepsin ($p=0,002$) and MEDS score ($p=0,002$). As an especially conceived tool (MEDS stands for Mortality in Emergency Department in Sepsis) was not surprisingly associated with mortality, while presepsin was found to have also a strong correlation with mortality, this being also reported in other studies^(10,11,12,13).

In cancer patients, MEDS showed a strong correlation ($p=0,02$) with mortality, while in diabetes mellitus presepsin ($p=0,011$) and MEDS ($p=0,061$) were significantly correlated with mortality. In renal and cardiac failure presepsin was a significantly prognostic factor with $p=0,034$ and respectively $0,015$; also, creatinine clearance $p=0,0001$ respectively $0,002$ was an important prognostic factor. For the patients with respiratory insufficiency NEWS2 ($p=0,006$) and MEDS score ($p=0,001$) were found to have significant statistical correlation.

Discussions

In the present study we tried to assess the impact of comorbidities over mortality and also to see how a promising biomarker (presepsin) and clinical scores (NEWS2 and MEDS) have an impact over prognosis in

different pathological conditions. Surprisingly, the institutionalized patients had an ominous prognostic and somehow expected, the respiratory failure. Other frequent pathologies (malignancy, diabetes mellitus, cardiac failure, renal failure), also very important, had a lesser impact on mortality, due to a variety of life supporting treatments. The age was not a significant factor, but close to that ($p=0,07$). Median age for death was $75,63 \pm 14,7$ while in survivors median age was $69,59 \pm 15,92$.

Sepsis, defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection⁽⁶⁾, is a clinical syndrome that can include a very heterogeneous population of critical ill patients⁽¹⁴⁾. Until now, progresses were made, classifications were changed, but the huge impact on patients on the medical systems show that much is to be done. Researchers sought to cure specific the sepsis, but only a minority of patients have only a sepsis and no other diseases.

The one-size fits it all treatment for sepsis with little or no emphasis on a particular patient is not found yet. Probably considering the wholeness of the patient with his pathogenic particularities would lead to a more expected outcome. Consequently, given the heterogeneity of the patients, the clinical trials for studying different treatments were not very well standardized⁽¹⁴⁾. This may lead to a heterogeneity of treatment effect, in which

Figure 1. Sex distribution in the study group

Figure 4. Presence of cardiac failure in the study group

Figure 2. Presence of cancer in the study group

Figure 5. Presence of renal failure in the study group

Figure 3. Presence of DM in the study group

Figure 6. Presence of respiratory failure in the study group

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	Death	Survival	p
Age	75,63±14,70	69,58±15,92	0,0780
Weight	70,51±16,16	71,73±11,70	0,6620
GCS	13,81±2,51	14,38±2,09	0,2310
MEDS	12,92±4,34	8,64±3,91	0,0000
QSOFA	1,14±1,13	0,54±0,89	0,0040
NEWS2	6,59±4,09	4,26±3,39	0,0030
HR	102,07±22,54	100,53±22,77	0,7550
SBP	109,03±29,42	118,84±29,01	0,1230
DBP	66,59±18,79	69,64±18,71	0,4410
RR	17,51±3,66	16,95±4,30	0,5390
SpO2	94,55±4,46	95,44±3,64	0,2890
Temperature	37,50±0,84	37,33±1,09	0,5580
WBC	23,35±15,95	18,76±13,40	0,1350
PSP	3272,59±4457,07	2407,81±2569,82	0,1970
Creatinine	2,61±1,54	2,43±2,23	0,6940
BUN	126,25±64,68	97,15±74,03	0,0670
Hb	10,97±2,72	11,58±2,79	0,3150
PLT	299,96±214,21	260,69±173,96	0,3280
Na	134,77±9,36	133,20±7,39	0,3600
K	4,67±0,97	4,15±0,96	0,0150
ALT	58,85±83,28	59,10±99,24	0,9900
AST	114,11±1,44	1,88±2,04	0,2230
TBR	1,67±1,44	1,88±2,04	0,6270
Glu	145,40±69,76	146,37±76,93	0,9530

Table 2. The impact of different parameters on mortality

Figure 7. Mortality rate in patients with/without cancer ($p=ns$)

Figure 10. Mortality rate in patients with/without renal failure ($p=ns$)

Figure 8. Mortality rate in patients with/without diabetes ($p=ns$)

Figure 11. Mortality rate in patients with/without respiratory failure ($p=0.03$)

Figure 9. Mortality rate in patients with/without cardiac failure ($p=ns$)

Figure 12. Mortality rate in patients from nursing home vs. no nursing home ($p=0.0001$)

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	Malignancy			DM			CF		
	Yes	No	p	Yes	No	p	Yes	No	p
qSOFA	0,628	0,688	0,759	0,740	0,653	0,683	0,530	0,763	0,197
NEWS2	4,4	4,911	0,486	5,518	4,561	0,231	4,224	5,118	0,185
PSP	2820,029	2506,944	0,611	4475,556	2076,388	0,000	3317,286	2128,671	0,034
MEDS	11,457	8,333	0,02	10,962	9,183	0,061	9,979	9,302	0,400

KF			RF			Institutionalized patients		
Yes	No	p	Yes	No	p	Yes	No	p
0,500	0,741	0,103	1,000	0,609	0,103	1,00	0,652	0,365
4,611	4,831	0,060	6,800	4,380	0,006	6,571	4,661	0,182
3644,361	2169,9809	0,475	2141,850	2680,848	0,475	6024,286	2391,153	0,002
10,194	9,314	0,001	12,55	9,000	0,001	14,428	9,279	0,002

Table 3. Various scores and the impact on comorbidities.

some patients benefit from a specific intervention whereas others are harmed and the overall effect of that intervention appears ineffective¹⁵. The present study has a number of limitations. A single centre retrospective, observational study may not have surprised the full impact on comorbidities on mortality. Also, the size of the cohort may have not the power requested to draw final conclusions. Future studies should include more patients from different sites. Our hospital, being a tertiary hospital, may have had more than normal complex patients, which can have an impact on generalizing conclusions. In addition, the retrospective nature of the work may have contributed to the lower-than-expected interrater agreement.

As strengths in our study we found that some not well studied factors may have a big impact on mortality (institutionalized patients, respiratory insufficiency) while better treatments on diabetes mellitus, cardiac and renal failure were not an immediate cause of death. Further research is still to be done.

Conclusions

In the present study, we tried to study the impact of comorbidities on sepsis and found that institutionalized patients without any other comorbidities are in itself an ominous factor. Furthermore, the respiratory failure was found to have a big impact on mortality. A combination of different scores and biomarkers can also predict the prognostic with significant accuracy.

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