Prognostic factors in older patients admitted in ICU with diagnosis of abdominal sepsis (sepsis-3 criteria)

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INTRODUCTION

Sepsis and septic shock are major health problems: worldwide, millions of people are affected every year, with an overall mortality rate exceeding 25%. Sepsis is also one of the first causes of death in older patients. The incidence of sepsis is growing, as a result of the increase in the mean population age, with consequent increase in comorbidities, and greater efficacy in diagnosis.1,2 Age plays a key role as independent prognostic factor for morbidity and mortality in septic patients: early intra-hospital mortality is more frequent in elderly patients, while, among survivors, disability is more likely.3

Background & aims. In septic older patients, hospitalization in Intensive Care Unit (ICU) is often associated with unfavourable outcomes. The aim of this study was to estimate the prevalence of geriatric age in patients admitted to ICU for abdominal sepsis and to investigate predictors of mortality, including quickSOFA, a recent prognostic index proposed for septic patients.

Methods. Prospective observational study on patients admitted to ICU of St. Anna Hospital (Ferrara) between January and July 2016 with the following inclusion criteria: 1) adults (18 years); 2) abdominal infection treated with surgically techniques; 3) admission to ICU. Demographic, clinical data and survival at 30 and 90-day were collected for each patient.

Results. Thirty patients were enrolled, and the majority of geriatric patients (80% ≥ 65 years and 53% ≥ 75 years). The 30 and 90-day mortality was 17 and 37%, respectively. Almost all deaths occurred in older age (mortality rate of 42%). SOFA (Sepsis Related Organ Failure Assessment) score was the prognostic index most frequently associated with exitus at 30 (AUC = 0.702) and 90 days (AUC = 0.730). quickSOFA was only related to early mortality (AUC = 0.640).

Conclusions. Our data confirm the high geriatric prevalence among patients admitted to ICU for abdominal sepsis, underlining the advanced age as a negative prognostic factor. SOFA score appears a reliable prognostic indicator of mortality, also in older population, while quickSOFA proved effective only for short-term mortality.

Key words: elderly, abdominal sepsis, intensive care, quickSOFA
The diagnosis of sepsis is complex, due to the high variability of the clinical picture and the lack of pathognomonic signs or symptoms. To promote an early identification and a timely treatment, crucial for prognosis, in 2016, current definitions of sepsis and septic shock were modified by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) \(^4,5\). Sepsis was re-defined as a syndrome characterized by one or more life-threatening organ dysfunctions, due to an altered host’s response to infection. Therefore, sepsis should be diagnosed from an acute increase of 2 or more SOFA points (compared to the patient’s basic conditions). SOFA score is a system to assess the presence and the grade of organ failure, created on septic patients admitted to ICU \(^6\). An increase in SOFA points is correlated to a higher risk of mortality \(^7\). The SOFA score is calculated based on 6 physiological variables, that are index of the degree of a system’s function (cardiocirculatory, respiratory, renal, hepatic, coagulative and nervous). Furthermore, each of these variables is given a score from 0 (normal) to 4 (seriously compromised), according to the criteria shown in Table I. The SOFA score can be re-calculated every 24 hours to monitor the patient’s clinical evolution in ICU \(^6\).

On the other hand, septic shock is identified in a septic patient (SOFA ≥ 2) who has persistent hypotension, despite of an adequate fluid therapy, which requires the administration of vasoactive amines, in order to maintain a Mean Arterial Pressure (MAP) > 65 mmHg, and a with serum lactate levels > 2 mmol/L. Under these septic shock evaluation criteria, hospital mortality was reported to be higher than 40% \(^4\). In addition, to better identify patients with the highest death risk from sepsis, a new prognostic score was introduced as a modified version of SOFA. This new score, called quickSOFA (qSOFA), it is expected to be simple and easily accessible to healthcare personnel, even outside the hospital, since it does not require any laboratory test. Specifically, three clinical parameters are evaluated: tachypnea (Respiratory Rate ≥ 22/min), altered mental status (Glasgow Coma Scale ≤ 14) and arterial hypotension (Systolic Arterial Pressure ≤ 100 mmHg). A binary score, 0/1, is assigned to each one of these parameters, so that the maximum overall qSOFA score is 3. A qSOFA ≥ 2 is associated with a high risk of mortality due to sepsis. Previous studies reported a higher risk of mortality of 8% in patients with qSOFA equal to 2 and greater than 20% with qSOFA equal to 3 \(^4\). However, the qSOFA still needs a prospective validation to confirm its real efficacy, as it was created on retrospective studies on acute patients, without any distinction by age.

Among the different origin sites of sepsis and septic shock, the intra-abdominal infection is the second most frequent cause in critically ill patients (20-25% of total), after pulmonary infections. According to several studies carried out in an Intensive Care Setting \(^8\), 51% of all patients admitted is infected and 19% of these have an intra-abdominal infection. Abdominal sepsis is a complication of intra-abdominal infection characterized by

### Table I. Sequential [sepsis related] Organ Failure Assessment (SOFA) Score.

<table>
<thead>
<tr>
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<th>Score</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
<td></td>
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<tr>
<td>PaO2/FiO2 (mmHg)</td>
<td>≥ 400</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
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<tr>
<td>Platelets x 10^9/μL</td>
<td>≥ 150</td>
</tr>
<tr>
<td><strong>Hepatic system</strong></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 1.2</td>
</tr>
<tr>
<td><strong>Cardiovascular system</strong></td>
<td></td>
</tr>
<tr>
<td>MAP ≥ 70 mmHg</td>
<td>MAP &lt; 70 mmHg</td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
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<tr>
<td>Glasgow Coma Scale</td>
<td>15</td>
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<tr>
<td><strong>Renal system</strong></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>&lt; 1.2</td>
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<tr>
<td>Urine output (ml/day)</td>
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</table>

Abbreviations: PaO2, partial pressure of oxygen; FiO 2, fraction of inspired oxygen; MAP, mean arterial pressure.
Notes: \(a\) All catecholamines doses represent μg/kg/min.
the highest rate of deaths (30 to 60%), as compared to those of other primitive sites.\textsuperscript{9,10}

The literature currently available on this subject is extremely limited and there are no randomized controlled trials regarding the efficacy of qSOFA as prognostic score in older population affected by abdominal sepsis. In a recent prospective study performed on 272 older patients with sepsis, admitted in ICU, qSOFA seems to be ineffective to predict intra-hospital, while seems to be correlated to mortality three months after discharge.\textsuperscript{11} Moreover, a retrospective cohort study, published in 2018 and performed in Finland, has shown an insufficient sensitivity of qSOFA as prognostic score in septic adult population with a diffuse secondary peritonitis, without any age distinction.\textsuperscript{12}

Among the recent guidelines recommended for abdominal sepsis management, in addition to a surgical source control and an intensive support of organ function,\textsuperscript{13} it is necessary to start timely an appropriate antimicrobial therapy at high doses, namely effective on the microorganisms that sustain the infection.\textsuperscript{14,15}

The present study is aimed to analyze predictors of mortality for sepsis, in particular testing qSOFA as score for negative outcomes in older patients with abdominal sepsis admitted in ICU.

\section*{MATERIALS AND METHODS}

This is a prospective observational study carried out in the Intensive Care Unit (ICU) of St. Anna Hospital (Ferrara), between January and July 2016. The study enrolled patients admitted to ICU with all the following inclusion criteria: 1) adults (\( \geq 18 \) years); 2) presence of abdominal infection treated with percutaneous or surgically techniques; 3) admission to ICU for abdominal sepsis. The initial diagnosis of sepsis was carried out through the 2001 criteria; subsequently, these criteria were compared with sepsis-3 criteria through a post-hoc analysis.\textsuperscript{4} Patients < 18 year-old and pregnant women were excluded.

For each patient, the following data were collected:

a) demographic information: age, sex, weight and height;

b) admission to ICU: date, type of admission (medical, surgical in election, emergency surgery), the most common comorbidities (cancer, chronic renal failure, heart failure, diabetes, obesity);

c) diagnosis of abdominal sepsis: diagnostic tools (clinical, abdominal X-ray, abdominal Ultrasound, exploratory laparoscopy, exploratory laparotomy), anatomical integrity (presence or absence of perforation – localized or diffuse peritonitis), diagnosis (primary – secondary – tertiary peritonitis);

d) microbiology: cultures with antibiogram either on intra- and postoperative peritoneal fluid (on surgical wound tampons), or on BronchoAlveolar Lavage (BAL), or on urine/ blood cultures, distinguished among multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria;\textsuperscript{16}

e) anti-infective treatment: antimicrobial therapy: drug, daily dose, type of administration (intermittent intravenous, continuous intravenous, oral, intramuscular), duration, type of prescription (empirical or targeted); source control: drainage techniques (percutaneous drainage without surgery, surgical drainage, peritoneal lavage, post-operative drainage), necrotic tissue resection, decompression with laparostomy, reconstruction of normal anatomy; use of additional sepsis therapies: immunoglobulins, hydrocortisone, others;

f) severity of sepsis: in preoperative period (6 hours before surgery), in early post-operative period (24 hours after surgery) and in late post-operative (72 hours after the surgery). The diagnosis was performed evaluating: SOFA score, organ support (mechanical ventilation, vasoactive amines, dialysis), pH, serum lactates, C-reactive protein (CRP), procalcitonin (PCT), white blood cells;

g) fluid balance during the first 5 days of ICU admission;

h) 30-day and 90-day survival. The primary outcome was 90-day mortality (intermediate term mortality); secondary outcomes were 30-day mortality (short term mortality), duration of antibiotic therapy and duration of hospitalization in ICU.

\section*{Statistical analysis}

The results are reported as mean ± standard deviation, median [interquartile range], relative risk and 95% confidence interval, when appropriate. The normality of the distribution was evaluated with Shapiro-Wilk test. The continuous variables were compared by means of the t-test or the Mann-Whitney test, depending on the distribution of data (normal or not normal). Repeated data were processed with ANOVA test for repeated measurements with post-hoc Šidák correction. The categorical variables were compared through the Fisher’s exact test. The analysis for repeated measurements was performed using the Kruskal-Wallis test for not normally distributed samples. Values with \( p \)-value < 0.05 were considered statistically significant. The predictive performance of each score was assessed with AUC analysis. In accordance with the guidelines, scores were classified as non-predictive (AUC = 0.5), inaccurate (0.5 < AUC < 0.7), moderately accurate (0.7 ≤ AUC < 0.9), extremely accurate (0.9 ≤ AUC < 1) and perfect (AUC = 1).
RESULTS

During the observational study period, thirty patients were enrolled. The clinical and demographic characteristics of the population before and after admission to ICU are summarized in Tables II-IV. Among the patients admitted to ICU with abdominal sepsis, 80% was aged ≥ 65 (24 out of 30) and 53% ≥ 75 years (17 out of 30). Regarding overall mortality, 30-day mortality was 17% (n = 5) and 90-day mortality was 37% (n = 11). All hospitalized patients were affected by pre-existing comorbidities, the most common of which are reported in Table II. Among these, chronic renal failure and diabetes mellitus were more common among patients who died during the follow-up (6/11 vs 1/19 and 2/19, respectively, p < 0.05). Analyzing the rate of death in the different age classes, almost all patients who died were ≥ 65 years old, in particular 27% were in the middle class of age (between 65 and 75 year) and 64% in the oldest class (≥ 75 years) (see Figure 1). No other significant difference in mortality was observed at baseline, except for the CRP levels that was directly associated with an increased risk of death (13 ± 5 vs 18.8 ± 8, p = 0.03). The postoperative data at 24 hours (Tab. III) and at 72 hours (Tab. IV) confirm an increased mortality linked to CRP values (at 24h: 17.0 [10.7-25.0] vs 26.0 [17.2-32.0], p = 0.01, at 72h: 16.6 ± 4.5 vs 24.0 ± 8.1, p = 0.06). The CRP trend is shown in Figure 2. No significant differences were found in mortality, in relation to neither the lactate levels (preoperative: 2.4 ± 1.8 vs 2.7 ± 1.1, p = 0.62; post-operative at 24h: 2.3 ± 1 vs 2.4 ± 1.1, p = 0.91, post-operative at 72h: 1.1 ± 0.5 vs 1.62 ± 0.6, p = 0.05) nor the levels of PCT, whose dosage was possible only in the postoperative period (at 24h: 7.0 [1.7-33.0] vs 9.1 [3.5-22.6], p = 0.14; at 72h: 6.0 [0.7-15.1] vs 10 [2.8-18.5], p = 0.10). In patients with septic shock, blood lactate levels show a trend towards normalization in survivor patients, although without reaching statistical significance (p = 0.11). The most frequent cause of abdominal sepsis was due to secondary peritonitis. In 57% of total cases, secondary peritonitis was due to bowel perforation or ischemia; the remaining cases were caused by postoperative peritonitis, gangrenous acute appendicitis, biliary tract infections or inflammatory bowel disease exacerbation. The most frequently isolated bacteria in different biological liquids were Escherichia coli (16 isolations), Pseudomonas aeruginosa (14 isolations) and Enterococcus faecium (12 isolations). Pathogens were more frequently isolated in peritoneal fluid (48 total isolations), followed by swabs on surgical wound; 11 isolations were obtained in blood culture. The only species isolated of fungus was Candida albicans, but less frequently with respect to bacteria: 8 isolations of this fungus were found.

SOFA score was the prognostic score better associated with mortality at 30 (AUC = 0.702) and at 90 days (AUC = 0.730). qSOFA was also somehow predictive of 30-day mortality (AUC = 0.640), but it did not show any correlation with 90-day mortality (AUC = 0.570). Among patients with positive cultures (70%), starting an appropriate antibiotic therapy within the first 12 hours from the diagnosis was strongly associated with a reduction in mortality (70 vs 12%, p = 0.01).

Table II. Characteristics of the population at baseline in relation with the primary outcome.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivor N = 19</th>
<th>Non survivor N = 11</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 years n,(%)</td>
<td>14 (73)</td>
<td>10 (91)</td>
<td>0.26</td>
</tr>
<tr>
<td>Gender (female) n,(%)</td>
<td>7 (37)</td>
<td>5 (45)</td>
<td>0.46</td>
</tr>
<tr>
<td>Chronic renal disease n,(%)</td>
<td>1 (5)</td>
<td>6 (54)</td>
<td>0.004</td>
</tr>
<tr>
<td>Heart failure n,(%)</td>
<td>1 (5)</td>
<td>1 (9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes mellitus n,(%)</td>
<td>2 (10)</td>
<td>6 (54)</td>
<td>0.015</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30) n,(%)</td>
<td>5 (26)</td>
<td>2 (18)</td>
<td>0.48</td>
</tr>
<tr>
<td>Neoplasia n,(%)</td>
<td>5 (26)</td>
<td>2 (18)</td>
<td>0.48</td>
</tr>
<tr>
<td>MV n,(%)</td>
<td>5 (26)</td>
<td>4 (36)</td>
<td>0.43</td>
</tr>
<tr>
<td>Inotropes n,(%)</td>
<td>0 (0)</td>
<td>1 (9)</td>
<td>0.37</td>
</tr>
<tr>
<td>qSOFA ≥ 2 n,(%)</td>
<td>6 (31)</td>
<td>5 (45)</td>
<td>0.35</td>
</tr>
<tr>
<td>Lac (mmol/L)</td>
<td>2.4 ± 1.8</td>
<td>2.7 ± 1.1</td>
<td>0.62</td>
</tr>
<tr>
<td>pH</td>
<td>7.1 ± 0.3</td>
<td>7.0 ± 0.1</td>
<td>0.19</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>13 ± 5</td>
<td>18.8 ± 8</td>
<td>0.03</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td>14.7 [10-22]</td>
<td>12.6 [12-18]</td>
<td>0.61</td>
</tr>
<tr>
<td>SOFA score</td>
<td>7.1 ± 3</td>
<td>7.55 ± 3.6</td>
<td>0.77</td>
</tr>
</tbody>
</table>

MV: mechanical ventilation; Lac: serum lactates; CRP: C reactive protein; WBC: white blood cells

Figure 1. 90-day mortality rate (%) in relation to age (y). * p = 0.37; + p = 1; § p = 0.47.
of hospitalization; however, after 72 hours, the fluidic balance was statistically different (p < 0.001), resulting higher in patients who died.

**DISCUSSION**

The main result of this study is that our data confirm the high prevalence of very old patients admitted to ICU for abdominal sepsis. Moreover, the current study shows the high mortality due to this pathology (37% of our sample) 17, especially among older persons: indeed, almost all deaths occurred in patients ≥ 65 years, and more than half of patients ≥ 75 years died. Therefore, as already reported in the literature 3, advanced age seems to predict an adverse outcome in patients with abdominal sepsis. Besides, this study demonstrated that SOFA score is associated with short and intermediate term mortality supporting its use as prognostic marker.

The comorbidities can be considered as an additional risk factor for failure to control the infection; in our study, those more correlated to a negative outcome were chronic renal insufficiency 18 and mellitus diabetes 19. Although CRP is recognized as a non-specific index, high CRP levels in septic patients seem correlated to a higher mortality: during the three days of this survey, CRP trend appears to be significantly different between patients who died and not (Fig. 2). Instead, in contrast with the literature 20,21, neither PCT nor serum lactate levels were related to sepsis severity and mortality. During the first and the third post-operative day, PCT trend shows a lower decrease in patients who died, as

![Figure 2. CRP levels (mg/dl) in the preoperative day (Day 1), in the first (Day 2) and third (Day 3) postoperative day in the recruited population divided in survivor and non-survivor. * p = 0.03; + p = 0.01; § p = 0.06.](image_url)
Prognostic factors in older patients admitted in ICU with diagnosis of abdominal sepsis (sepsis-3 criteria)

Typically, in septic patients, the fluidic balance is enormous; however, as already observed, our data demonstrate that the fluidic therapy is beneficial for the outcome. Among patients who died, but again without statistical significance (Tabs. II–IV). These results are likely due to the small sample size and the high heterogeneity of patients’ characteristics (age, comorbidity, bacteria causing the infection, use of invasive devices); for instance, serum lactate analysis was carried out only on the subgroup of patients with septic shock, further reducing the statistical power of the analysis.

In agreement with previous studies, the SOFA score proved a reliable prognostic score of mortality in geriatric patients, whereas the qSOFA, created on retrospective studies, was related to mortality risk only at 30 days, suggesting that qSOFA needs further validation studies as a prognostic mortality score for sepsis, particularly in the geriatric population. In accordance with several publications, our data demonstrate how an appropriate empirical antibiotic therapy, established in the first 12 hours after diagnosis, leads to a reduction in overall mortality from 70 to 12% (p = 0.01). Thus, a previous hypothesis on the type of bacterium causing the sepsis would be very important, investigating the most common local antibiotic resistances; this procedure highly increases the success probability of the empirical antibiotic therapy with an enormous benefit for the outcome. Among patients with at least one positive culture, 91% had a polymicrobial infection as etiological cause of abdominal sepsis, recognized by the literature as a highly negative prognostic factor. The most frequently isolated bacteria were E. coli, in particular from peritoneal fluid, and P. aeruginosa, often found in different biological samples, the latter a clear sign of the higher tendency of Pseudomonas infection to spread out. Enterococci were also very frequent, particularly E. faecium. Moreover, according to the literature, the present investigation confirmed that abdominal sepsis is less frequently caused by fungi; among them, only C. albicans was isolated and it was always sensitive.

In addition to an early and appropriate antibiotic therapy, one of the most important recommendations of Surviving Sepsis Campaign is an aggressive intravenous fluids administration, in order to maintain an arterial pressure sufficient to guarantee adequate tissue perfusion. Typically, in septic patients, the fluidic balance is enormously positive, because of the increased permeability of blood capillary wall, especially during the first hours of fluid-therapy. However, as already observed, our results also show an increased mortality in patients with positive fluid balance prolonged over time, in particular over 72 hours: a very positive fluidic balance from the fourth day onwards correlates to an increased mortality in septic patients.

It is worth underlining that qSOFA was created on retrospective studies performed on patients with an median age of 60 years and thus requires a prospective validation on older population for its use in everyday clinical life. The major strength of our study is that this validation is, at least partially, given by the present investigation, a prospective study which analyses qSOFA in a septic population. However, the small sample size (30 patients) with high heterogeneity in clinical characteristics is the main limit of our study. As consequence, this study should be considered as a preliminary report that needs more detailed future investigations to validate the clinical use of qSOFA as prognostic tool in older people with diagnosis of sepsis.

In conclusion, our results confirm the high mortality caused by abdominal sepsis in geriatric patient. Almost all deaths occurred in patients ≥ 65 years old, underlining as age is a negative prognostic factor during abdominal sepsis. Even in older persons with sepsis, SOFA is a reliable score of mortality, while qSOFA appears to be correlated to 30-days mortality and it could be useful in extra-hospital setting to discriminate patients with an increased risk of death for sepsis.

References

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