



Assessment of clinical outcome of children with sepsis outside the intensive care unit

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Abstract

In 2016, in order to identify adult patients with sepsis who are likely to have poor outcomes, the Third International Consensus Definitions Task Force introduced a new bedside index, called the quick Sepsis-related Organ Failure Assessment (qSOFA) score. However, these new criteria have not been validated in the pediatric population. In this study, we sought to assess the qSOFA score for children with sepsis, who are being treated outside the pediatric intensive care units. The qSOFA criteria were revised and applied to a study population of 89 pediatric patients with sepsis, admitted in a pediatric tertiary referral center from 2006 to 2016. The analysis of prognostic performance of qSOFA score for the prediction of severe sepsis showed a sensitivity of 46% (95% CI, 27–67%), a specificity of 74% (95% CI, 62–85%), a positive predictive value of 43% (95% CI, 34–52%), and a negative predictive value of 77% (95% CI, 71–82%). The area under ROC curve for qSOFA score ≥ 2 was 0.602 (95% CI 0.492–0.705).

Conclusion: The qSOFA score showed a low accuracy to identify children in the pediatric ward at risk for severe sepsis. Clinical tools are needed to facilitate the diagnosis of impending organ dysfunction in pediatric infection outside of the ICU.

What is Known:

- One of the major challenges for clinicians is to identify and recognize children with sepsis and impending organ dysfunction, in the emergency and in the pediatric department.
- In 2016, members of the Sepsis-3 task force proposed qSOFA, an empirically derived score using simple clinical criteria, to assist clinicians in identifying adult patients with sepsis at risk for poor outcome.

What is New:

- qSOFA demonstrated insufficient clinical value to be recommended as a screening tool for pediatric sepsis outside ICU.
- D-dimer level and blood glucose may be useful biomarkers to identify children at risk for severe sepsis.

Keywords Pediatric sepsis · qSOFA · Impending organ dysfunction · Pediatric infection · Severe sepsis

Abbreviations

BP	Blood pressure
ICU	Intensive care units
IQR	Interquartile range
NPV	Negative predictive values
PPV	Positive predictive values

PICU	Pediatric intensive care units
qSOFA	Quick Sepsis-related Organ Failure Assessment
PSCC	Pediatric Sepsis Consensus Congress
ROC	Receiver operating characteristic
SD	Standard deviation
SE	Sensibility

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SIRS	Systemic inflammatory response syndrome
SOFA	Sequential [Sepsis-related] Organ Failure Assessment
SP	Specificity
SS	Severe sepsis

Introduction

Sepsis is a clinical syndrome resulting from a dysregulated systemic inflammatory response to infection, associated with a poor outcome, including high short-term mortality. A recent systematic review and meta-analysis estimate an incidence of 3.0 million cases of sepsis in neonates and 1.2 million cases in children younger than 20 years annually. Mortality ranged from 1 to 5% for sepsis and 9 to 20% for severe sepsis (SS) [8].

It is quite complicated for clinicians to diagnose and assess pediatric sepsis due to the lack of specific signs and symptoms and the rapid deterioration that occurs when compensation fails. Children who develop signs of severe sepsis with organ dysfunction, and especially those who develop septic shock, are at the highest risk of life-threatening and fatal complications.

In 2005, the Pediatric Sepsis Consensus Congress (PSCC) [10] agreed that the definition of pediatric sepsis requires the presence of systemic inflammatory response syndrome (SIRS) in a child with suspected or proven infection. In the light of the high mortality associated with sepsis, the importance of early detection and intervention was emphasized. However, SIRS criteria have been criticized for their poor specificity because these are also met by children with non-infectious diseases; furthermore, even infected children meeting these criteria often have no organ dysfunction [28, 30].

In 2016, a joint SCCM/European Society of Intensive Care Medicine task force developed new definitions of adult sepsis and clinical criteria to identify patients likely to have this deadly disorder (Sepsis-3 criteria) [32]. Sepsis, for adult patients, is now defined as a “life-threatening organ dysfunction caused by a dysregulated host response to infection” and it is identified by an increase of, at least, two points in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score in patients with a suspicion of infection. The quick SOFA (qSOFA) score, a surrogate for SOFA in settings in which all components of SOFA are not routinely measured, was proposed to help identify patients with suspected infection who are being treated outside critical care units and likely to develop complications of sepsis.

Recently, a pediatric version of the SOFA score (pSOFA) was adapted and examined in a single-center retrospective study [21]. The authors found that the pSOFA score showed an excellent discrimination for in-hospital mortality in a general pediatric intensive care units (PICU) population, 21 years

or younger. This finding was confirmed in a recent prospective multicentric cohort study of children admitted in ICU for infections [28]. The authors reported that the qSOFA score, adapted according to age-specific cutoff, showed moderate accuracy to identify infected children at risk for worse outcome.

However, Sepsis-3-based criteria have never been evaluated in pediatric wards, outside intensive care settings. Moreover, to assist with early recognition of organ dysfunction, others pediatric sepsis screening scores have been developed but they were validated only in the PICU setting and not recognized outside the PICU, where simpler tools, which include clinical variables that are easily obtained in the first hour, are needed [17, 24].

In this study, we sought to assess the qSOFA score for children with sepsis, outside the PICU. In addition, we sought to identify indicators that may be used for risk assessment in children. Finally, we provided etiological factors and the clinical characteristics of sepsis in children.

Materials and methods

Study population

Medical records of children admitted to the Tertiary Center of Pediatrics and Infectious Disease Unit, G. Salesi Children’s Hospital (Ancona, Italy) from January 1, 2006, to December 31, 2016, were retrospectively reviewed. The G. Salesi Children’s Hospital is one of the largest pediatric healthcare institutes in central and southern Italy and is a reference center for the care of children with infectious disease.

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge diagnosis codes for sepsis (995.91); neonatal sepsis (771.81); severe sepsis (995.92), septic shock (785.52), and septicemia (038.9) were used to generate lists of potential cases. A target samples size of 129 records was selected.

Data were collected on age, sex, history, clinical manifestations, laboratory investigations, and microbiological tests. Clinical and laboratory markers were taken in the first 24 h after sepsis onset, except for D-dimer that was collected at their worst value at any time during hospital stay. The onset time for sepsis was defined as the earliest time during a hospital encounter when the patient meets criteria for sepsis.

Children with sepsis were diagnosed according to the criteria of SIRS, sepsis, SS, and septic shock by the PSCC in 2005 [10].

Neonates that were less than 72 h old were excluded from the analysis.

The criteria of qSOFA score [32] were revised and applied for children, it included three parameters: respiratory rate > 95th percentile for the age (1 point); Glasgow Coma Scale

score of less than 15 (1 point); decrease in systolic blood pressure (BP) < 5th percentile for the age (1 point). The qSOFA scores were defined by applying age-specific cutoffs for respiratory rate and systolic blood pressure, as per the PSCC definitions [10, 11].

For each recruited patient, the three components of the qSOFA were collected at their highest level in the first 24 h.

The primary outcome was defined as development of severe sepsis (SS). In addition, secondary outcomes, defined as ICU admission, days of hospitalization, antibiotic treatment, and duration of fever, were stratified for qSOFA score and SS.

Statistical analysis

Statistical comparisons were assessed for discrete and continuous variables as appropriate. All non-normally distributed variables were expressed as median and interquartile range (IQR). Categorical variables were expressed as absolute number and percentage. Data non-normally distributed were analyzed using the Mann–Whitney *U* test, chi-square test (or Fisher's exact test) to compare continuous and dichotomous variables respectively. To assess the performances of the qSOFA in order to predict SS, we calculated diagnostic performances: sensitivity (SE), specificity (SP), and negative and positive predictive values (NPV and PPV) for a qSOFA score of 2 or higher. A receiver operating characteristic (ROC) curve was constructed and the corresponding area under the ROC curve (AUROC) calculated. Furthermore, performance of qSOFA to predict admission in ICU was compared with the definition of SS, established by the PSCC in 2005 [10]. The ROC curves were also obtained for the D-dimer and blood glucose values as predictors of SS. To determine the most appropriate cutoff value, which has the maximum sensitivity and specificity pair, Youden's index was calculated.

All statistical analyses were 2-tailed and *p* value < 0.05 was considered significant.

For the lack of previous studies on qSOFA in children with sepsis, the sample size was calculated based on the results of a previous study on adult data [9] looking for an in-hospital mortality rate of at least 10%. The sample size was determined to be 88 subjects assuming a power of 80% and confidence interval of 95%. The study period was extended to achieve the stated patient number.

All analyses were performed using the statistical software package SPSS software Version 20.0.

Ethical clearance

The local ethics committee, CER (Regional Ethics Committee of Marche), approved this single-center retrospective study (reference number 2017-0064 OR). The research was carried out in compliance with the Helsinki Declaration.

Results

Description of the study population

Over the study period, 129 patient files were identified. Twenty-nine (23%) neonates were excluded because they were affected by early onset sepsis, 11 (9%) children were excluded because they did not fulfill the criteria of sepsis, leaving 89 (69%) included for the final analysis (Fig. 1). Baseline characteristics of the study population are summarized in Table 1.

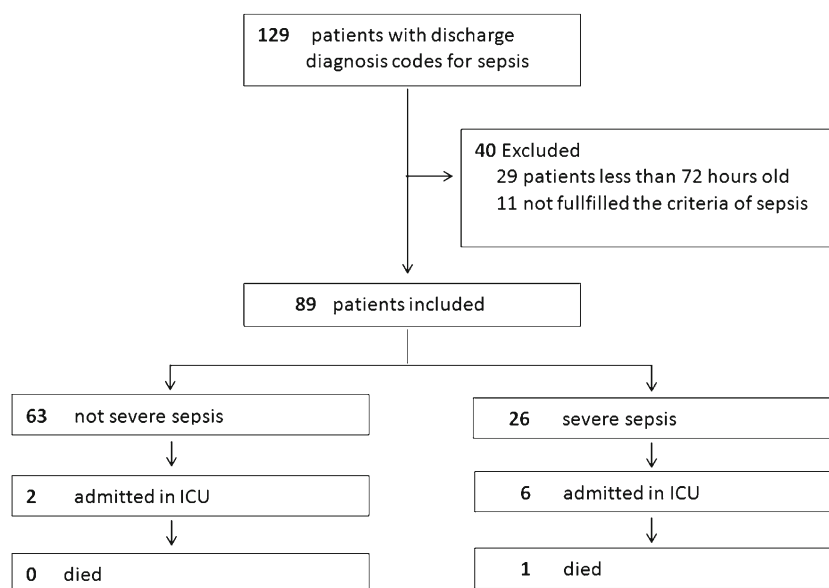
At least one comorbidity was present in 5 (6%) patients: three children were affected by hematology-oncology diseases (Hodgkin disease in complete remission, acute lymphoblastic leukemia in maintenance therapy, and cyclic neutropenia in therapy with granulokine, respectively); one patient by congenital heart disease (septal atrial defect in hemodynamic compensation), one patient by HIV infection (CD4 count on admission: 509 cell/mm³). Only one patient died and he was the patient affected by cyclic neutropenia. Twenty-six patients (29%) fulfilled the criteria of severe sepsis.

Etiological factors

In all patients, a bacterial culture, at least, was performed. A pathogen was identified in blood culture in 23/70 (33%), urine culture in 9/48 (19%), cerebrospinal fluid in 23/51 (45%), stool culture in 2/22 (9%), and swab culture in 7/12 (58%) of patients. The most commonly isolated bacteria are described in Table 2. A bacterial infection was documented from sterile sites in 42 (47%) patients. Viral diagnostics was performed in 37 (42%) patients. An exclusive viral infection was found in 4 (5%) patients. A combined infection (bacterial and viral) was identified in 2 (2%) patients. A patient was affected by fungal sepsis (*Candida albicans*). In 37 (42%) of 89 patients, sepsis was diagnosed but no pathogen was isolated. The sites of infection are described in Table 3.

Clinical and laboratoristic characteristics stratified for severe sepsis

As shown in Table 4, children baseline characteristics with non-SS were compared to those with SS, according to the criteria of PSCC [10]. Children with SS showed more frequent tachypnea and abnormal heart rate as clinical sign of onset respect to patients with non-SS (*p* = 0.004 and *p* = 0.01, respectively). The levels of D-dimer and blood glucose were significantly higher in patients with SS compared to non-SS (*p* = 0.001 and *p* = 0.003, respectively) (Table 4).

Fig. 1 Flow diagram showing study enrollment

Performance of qSOFA score for the prediction of severe sepsis

For patients with a qSOFA score < 2, the percentage of SS was 23% vs 43% with a qSOFA score of 2 or higher ($p = 0.1$). The AUROC curve for qSOFA was 0.602 (95% CI 0.492–0.705) (Fig. 2). For the prediction of SS, qSOFA score had a SE of 46% (95% CI, 27–67%), SP of 74% (95% CI, 62–85%), PPV of 43% (95% CI, 34–52%), and NPV of 77% (95% CI, 71–82%).

Performance of D-dimer and blood glucose for the prediction of severe sepsis

As a marker of SS, the most appropriate D-dimer cutoff value, calculated using a ROC curve, was 2568 $\mu\text{g/l}$. The AUROC

was found to be 0.729 (95% CI, 0.618–0.823), with a SE of 68% (95% CI, 47–85%), SP of 78% (95% CI, 64–88%), PPV of 59% (95% CI, 39–77%), and NPV of 84% (95% CI, 71–93%).

The ROC analysis revealed that the serum glucose level of 130 mg/dl was the best cutoff value for predicting SS. The AUROC was found to be 0.720 (95% CI, 0.603–0.819), with a SE of 52% (95% CI, 30–74%), SP of 88% (95% CI, 77–96%), PPV of 65% (95% CI, 38–86%), and NPV of 82% (95% CI, 70–91%).

Secondary outcomes stratified for severe sepsis and qSOFA

Patients with SS, compared to non-SS, needed longer hospitalization, antibiotic treatment, and higher frequency of ICU

Table 1 Characteristic of study population

Characteristics	Number (percentage)	Missing data (%)
Males/females	58/31 (65%)	0 (0%)
Age, months	12 (1–75)	0 (0%)
Median (IQR)		
Mean respiratory rate > 2 SD	48 (54%)	3 (3%)
Tachycardia/bradycardia	21 (24%)	4 (4%)
Temperature > 38.5 °C or < 36 °C	73 (82%)	2 (2%)
Frequency of organ dysfunction		
Cardiovascular	7 (8%)	N/A
Respiratory	15 (17%)	N/A
Neurologic	53 (60%)	N/A
Hematologic	13 (15%)	N/A
Renal	2 (2%)	N/A
Hepatic	12 (13%)	N/A

N/A not applicable

Table 2 Bacteria isolated by cultures from 89 patients

Type of pathogens isolated	Number (percentage)
<i>Streptococcus pneumoniae</i>	7 (8%)
<i>Streptococcus</i> group B	4 (4%)
<i>Streptococcus</i> group A	1 (1%)
<i>Streptococcus</i> group F	1 (1%)
<i>Meningococcus</i> spp	8 (9%)
<i>Meningococcus</i> Y/W135	3 (3%)
<i>Meningococcus</i> B	2 (2%)
<i>Escherichia coli</i>	7 (8%)
<i>Staphylococcus</i> spp.	6 (7%)
<i>Pseudomonas aeruginosa</i>	2 (2%)
<i>Enterococcus</i> spp.	2 (2%)
<i>Klebsiella pneumoniae</i>	2 (2%)
Others	5 (6%)

admission. No significant differences in secondary end points were found between patients with qSOFA score ≥ 2 compared to qSOFA < 2 (Table 5).

Sensitivity analyses of qSOFA score and severe sepsis for the prediction of ICU admission

The percentage of children admitted in ICU was 17% (5/29) for patients with a qSOFA score ≥ 2 and 5% (3/60) for qSOFA score < 2 ($p = 0.07$). The qSOFA score ≥ 2 had a SE of 63% (95% CI, 25–92%), SP of 71% (95% CI, 60–81%), PPV of 18% (95% CI, 6–37%), and NPV of 95.0% (95% CI, 86–99%). The AUROC for the SS was 0,750 (95% CI, 0.646–0.836), for qSOFA score it was 0.669 (95% CI, 0.560–0.765) (Fig. 3).

Discussion

In 2016, members of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) task force proposed qSOFA, an empirically derived score using simple clinical criteria, to assist clinicians in identifying patients with

Table 3 Site of infection from 89 patients

Site of infection	Number (percentage)
Central nervous system infection	37 (42%)
Urinary tract infection	9 (10%)
Respiratory system infection	8 (9%)
Gastrointestinal system infection	4 (5%)
Infection with unknown site	30 (34%)
Miscellaneous infections ^a	10 (11%)

^a Includes skin and soft tissue infection (1 patient) and throat or mouth infection (seven patients)

sepsis at risk for poor outcome [32]. Apparently, the use of qSOFA score in the emergency department setting resulted in greater prognostic accuracy for in-hospital mortality than did either SIRS or SS [9]. Recently, a pediatric version of the SOFA score (pSOFA) was adapted and analyzed in critically ill children in PICU with confirmed or suspected infection. The study showed that pSOFA score had excellent discrimination for in-hospital mortality, with an AUC of 0.94 (95% CI, 0.92–0.95) [21]. However, the authors used a retrospective design and data from a single PICU therefore limiting generalizability of the findings.

To our knowledge the current study is the only pediatric study that assesses the validity of qSOFA score among pediatric patients presenting outside the PICU. The results of our study show that qSOFA score has a low prognostic accuracy to predict SS. Compared to criteria of SS, defined by the PSCC in 2005 [10], qSOFA has also a worse discriminative value for predicting ICU admission. These findings are in contrast with studies on adult population [6, 9]. Freund et al. [9] evaluated the predictive validity of qSOFA in a prospective study of adult patients with suspected infection presenting to the Emergency Department. The qSOFA performed better than SIRS criteria and SS to predict in-hospital mortality. In a recent study, Churpek et al. [6] found that qSOFA was more accurate than SIRS for predicting in-hospital mortality and ICU transfer; however, the same study showed a lower prognostic performance among patients with suspected infection outside the ICU. In another report, Raith et al. [26] evaluated the predictive validity of qSOFA in a retrospective analysis on adults and they found that the discriminatory performance of qSOFA in considering the outcome of hospital mortality or ICU length of stay of 3 or more days was not higher than SIRS performance. We speculate that the low accuracy of qSOFA in our pediatric population is due to the fact that SS can be present without a qSOFA score ≥ 2 . In fact, in our study, patients with a qSOFA < 2 were affected by different forms of organ dysfunction in addition to those defined by the qSOFA score, such as hematologic and hepatic dysfunctions (Table 5). In addition, arterial hypotension, as confirmed by our study (Table 4), remains a late sign of pediatric septic shock [4]. Therefore, qSOFA does not seem to be a useful and reliable tool for the pediatrician outside the ICU. The greatest concern is that this new sepsis score, in the pediatric population, underestimates intervention at early stages of sepsis when the syndrome may be most treatable.

Epidemiological studies concerning pediatric sepsis are few and most of them involved children admitted in the pediatric ICU. The Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study collected data on a large number of children with SS admitted to a PICU throughout 2013–2014 at 128 sites in 26 countries and it estimated a point prevalence of 8.2% in PICU [36]. A recent multicenter prospective study reported an incidence of neonatal and pediatric culture-

Table 4 Clinical and laboratory characteristics, collected on admission*, stratified for non-severe sepsis and severe sepsis, according to the criteria of International Pediatric Sepsis Consensus Conference 2005 [10, 11]

Characteristics	Non-severe sepsis (63)	Missing data (%)	Severe sepsis (26)	Missing data (%)	<i>p</i> value
Sex <i>N</i> (%)					
Males/females	39/24 (62%)	0 (0%)	19/7 (73%)	0 (0%)	0.3
Age, months [median (IQR)]	8 (1–71)	0 (0%)	17 (2–111)	0 (0%)	0.4
Respiratory rate > 2SD <i>N</i> (%)	27 (43%)	2 (3%)	21 (81%)	0 (0%)	0.004
Abnormal heart rate ^a <i>N</i> (%)	8 (13%)	3 (5%)	13 (50%)	0 (0%)	0.01
<i>T</i> > 38.5 °C or < 36 °C <i>N</i> (%)	51 (81%)	1 (2%)	22 (85%)	0 (0%)	0.8
Hypotension ^b <i>N</i> (%)	1 (2%)	6 (10%)	2 (8%)	1 (4%)	0.5
GCS < 15 <i>N</i> (%)	45 (71%)	0 (0%)	20 (77%)	0 (0%)	0.8
WBC(/mmc) median (IQR)	19,610 (7540–22,700)	0 (0%)	15,295 (6325–23,555)	0 (0%)	0.7
Leukocyte count abnormalities ^c	51 (81%)	0 (0%)	19 (73%)	0 (0%)	0.6
Serum sodium (mEq/l) median (IQR)	136 (134–138)	3 (5%)	137 (133–140)	1 (4%)	0.6
Serum potassium (mEq/l) median (IQR)	4.4 (4.1–5.0)	3 (5%)	3.7 (3.4–4.4)	1 (4%)	0.001
Serum calcium (mg/dl) median (IQR)	9.2 (8.6–9.7)	5 (8%)	8.5 (8.0–9.2)	2 (8%)	0.007
Blood glucose (mg/dl) median (IQR)	104 (83–120)	11 (17%)	133 (104–180)	5 (19%)	0.003
D-dimer (μg/l) median (IQR)	1032 (471–2506)	9 (14%)	3444 (1463–6070)	1 (4%)	0.001

RR respiratory rate, *T* temperature, GCS Glasgow Coma Scale

*D-dimer and blood pressure collected to their worst level.

^a Tachycardia, defined as a mean heart rate > 95th percentile for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-h time period or for children < 1 yr. old bradycardia, defined as a mean heart rate < 10th percentile for age in the absence of external vagal stimulus, blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-h time period.

^b Systolic BP < 5th percentile for age.

^c Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or 10% immature neutrophils.

proven bacterial sepsis of 25.1 per 100,000 children per year, with an average 30-day in-hospital mortality of 7%. Organ dysfunction was present in 39% of episodes. Sepsis incidence decreased by two-thirds (8.3 per 100,000) if organ dysfunction

rather than SIRS was used as the criterion and mortality increased to 17% when organ dysfunction was present [1].

In our study, SS accounted in about one-third (29%) of cases of sepsis admitted in 10 years in a pediatric ward, and this data confirms that sepsis remains a critical problem in children even outside the ICU. The wideness gap in hospital mortality (1–26%) reported in literature [1, 8, 25] may be associated to the methods used to identify sepsis (i.e., different administrative codes and different definitions). The low hospital mortality in our study (1%) may be due to the characteristics of the studied population selected in pediatric ward, outside the ICU and hemato-oncology unit. The only child who died was affected by cyclic neutropenia and it is known that mortality in children with comorbidity is higher [36].

In our study, children with SS showed more frequent tachypnea and abnormal heart rate as clinical sign of onset than patients without SS, which could be attributed to the pathophysiological mechanisms of organ system dysfunctions. Respiratory rate is increased in response to tissue hypoxia and metabolic acidosis. It is also a sign of primary focus of infection in lungs, or early acute respiratory distress syndrome [20]. Tachycardia occurs early in response to falling cardiac output and is the most significant physical findings in septic shock [14].

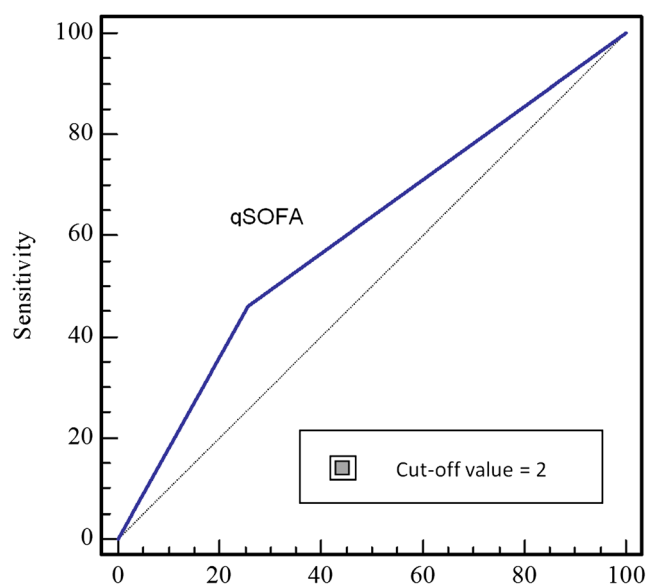


Fig. 2 ROC curves of qSOFA score for prediction of severe sepsis

Table 5 Secondary outcomes stratified for severe sepsis and qSOFA and frequency of organ dysfunction

Outcome	qSOFA score (<i>n</i>)			Severe sepsis (<i>n</i>)		
	< 2 (60)	≥ 2 (29)	<i>p</i> value	No (63)	Yes (26)	<i>p</i> value
ICU admission <i>N</i> (%)	3 (5%)	5 (17%)	0.071	2 (3%)	6 (23%)	0.007
Days of hospitalization [median (IQR)]	12 (10–21)	14 (11–46)	0.805	12 (10–20)	15 (12–39)	0.022
Duration of antibiotic treatment (days) [median (IQR)]	11 (8–15)	12 (4–16)	0.262	10 (7–14)	14 (11–23)	0.002
Duration of fever (hours) [median (IQR)]	48 (24–93)	48 (24–16)	0.254	48 (24–96)	60 (9–174)	0.6
Organ dysfunction						
Respiratory <i>N</i> (%)	7 (12%)	8 (28%)	0.143	0 (0%)	15 (58%)	< 0.001
Cardiovascular <i>N</i> (%)	2 (3%)	5 (17%)	0.075	0 (0%)	7 (27%)	< 0.001
Neurologic <i>N</i> (%)	33 (55%)	20 (69%)	0.455	32 (51%)	21 (81%)	0.010
Hematologic <i>N</i> (%)	6 (10%)	7 (24%)	0.179	1 (2%)	12 (46%)	< 0.001
Hepatic <i>N</i> (%)	7 (12%)	5 (17%)	0.765	2 (3%)	10 (38%)	< 0.001
Renal <i>N</i> (%)	1 (2%)	1 (3%)	1.000	0 (0%)	2 (8%)	0.1

According to previous studies [7, 19, 29] levels of D-dimer were higher in patients with SS than in those with non-SS and a significant correlation was found between D-dimer levels and days of hospitalization. Consumption and depletion of endogenous coagulation proteins occur frequently in patients with SS, and the depletion of anticoagulant and fibrinolytic factors contributes to the microvascular fibrin deposition associated with organ damage [2, 12, 15, 18].

Children with SS had higher blood glucose levels compared to children with non-SS (Table 4). Hyperglycemia was found to be associated with increased morbidity and mortality rates for both adults and children admitted to ICU [16, 22, 37]. Hyperglycemia was described as a marker of poor prognosis

in children after cardiac surgery, necrotizing enterocolitis (NEC), brain injury, and in mechanically ventilated children with bronchiolitis [5, 13, 31, 35, 38].

Our findings showed significant differences in calcium and potassium levels between SS and non-SS. Septic patients are particularly at risk of hypocalcemia and hypokalemia. In particular, increased mortality and longer stay in ICU were reported in patients with low ionized calcium [3, 23, 33, 34].

This study has some limitations which have to be pointed out.

First, the impact of our findings must be tempered by the relatively small sample size and the low number of children with severe sepsis that required admission to ICU. However, a recent study of Schlapbach et al. [28], involving children admitted to ICU due to infection, has obtained similar performance of the qSOFA.

Second, as suggest by Rhee et al. [27], the assignment of sepsis diagnoses is extremely variable among clinicians because there is no gold standard diagnostic test for sepsis. Therefore, the use of the ICD9-CM codes to select the population in the current retrospective study may have led to an overestimation of CNS infections and to an underestimation of respiratory infections and of the mortality for sepsis, limiting the generalizability of our findings.

Finally, data collected retrospectively means that analysis relied on medical records for all information and data could be incomplete. Indeed, many patients did not have blood lactate measurement, thus the latter was excluded from analysis, resulting in a possible misclassification in the septic shock category. The highest value of D-dimer level was recorded on different days among patients and the trend was not analyzed: this could have biased the results to higher D-dimer levels in SS group.

In conclusion, large-scale study has not been performed to refine pediatric sepsis screening tools. One of the major

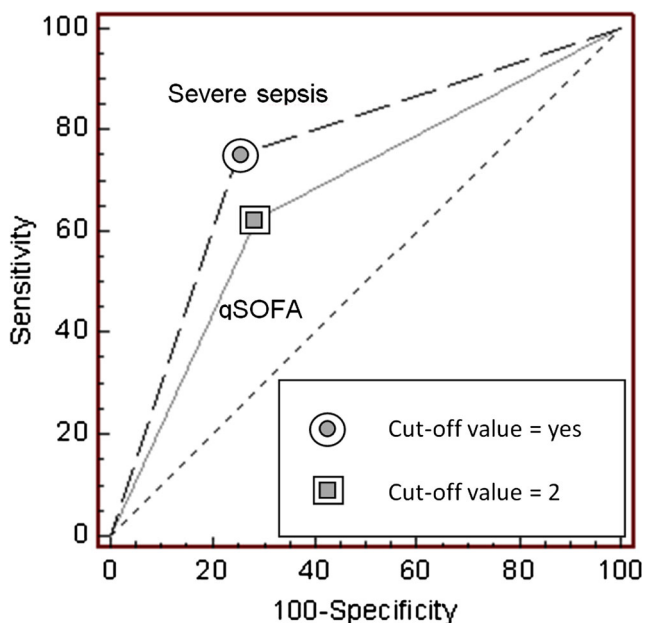


Fig. 3 ROC curves of qSOFA score and severe sepsis for prediction of admission in ICU

challenges for clinicians is to identify and recognize children with sepsis and impending organ dysfunction, in the pre-hospital setting, in the emergency and in the pediatric department. Contrary to adult patients, our data did not confirm the accuracy of the qSOFA score to stratify sepsis severity among pediatric patients. However, our study suggests, that D-dimer level and blood glucose may be useful biomarkers to identify children at risk for severe sepsis.

Authors' contributions All authors had full access to all of the data for this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

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

Ethical approval This retrospective study was approved by the Regional Ethics Committee of Marche (reference number 2017-0064 OR).

Informed consent For this type of study, formal consent is not required.

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