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Sepsis and septic shock in the Pediatric Intensive Care Unit (PICU): exploration of the diagnostic, therapeutic and prognostic factors of critically ill children with infection

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SUMMARY

LIST OF ACRONYMS AND ABBREVIATIONS

AUROC	Area Under Receiver Operating Characteristic
ACCM	American College of Critical Care Medicine
CRSS	Catecholamine-Refractory Septic Shock
FRSS	Fluid-Refractory Septic Shock
HICs	High-income Countries
ECMO	Extracorporeal Membrane Oxygenation
IPSCC	International Pediatric Sepsis Consensus Conference
IQR	Interquartile Range
LOS	Length of Stay
LICs	Low-Income Countries
LMICs	Lower-Middle Income Countries
MV	Mechanical Ventilation
OCSs	Observational Cohort Studies
PED	Pediatric Emergency Department
PICU	Pediatric Intensive Care Unit
PELOD	PEdiatric Logistic Organ Dysfunction
POPC	Pediatric Overall Performance Category
RCTs	Randomized Controlled Trials
RRT	Renal Replacement Therapy
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
UMICs	Upper-Middle Income Countries

SCIENTIFIC RATIONALE AND KNOWLEDGE GAPS

Septis and septic shock are leading cause of mortality and morbidity among children globally, thus requiring prompt diagnosis, intervention, and prognostication.

From an interventional point of view, the most severe patients that present with septic shock usually require fluid resuscitation to maintain adequate organ perfusion. In patients with Fluid-Refractory Septic Shock (FRSS), hemodynamic support with vasoactive agents is required. The choice of vasoactive agent is a critical decision in the management of these patients. According to the pediatric literature and up until now, *it's still unclear which first-line vasoactive agent is the best choice for pediatric patients with fluid-refractory septic shock*.

From a diagnostic and prognostic point of view, the definition of pediatric sepsis still relies on the Systemic Inflammatory Response Syndrome (SIRS) criteria, proposed in 2005 during the International Pediatric Sepsis Consensus Conference (IPSCC). Those criteria encompass nonspecific adaptative mechanisms (i.e., tachycardia, tachypnea) that are commonly seen in almost every febrile child. The validity of those criteria has been questioned multiple times in the recent adult literature, where they demonstrated insufficient sensitivity and specificity in identifying and stratyfing patients at risk for sepsis. For this reason, a joint taskforce from the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) has recently procedued a new definition of sepsis in adults, centering around the concept of organ dysfunction, and encapsulating this definition into the creation of the Sequential Organ Failure Assessment (SOFA) score. The SOFA score quantifies the degree of organ dysfunction, and it has shown to have a good performance in discriminating mortality among large cohorts of adult patients with sepsis. In children, despite recent attempts to create and validate pediatric versions of SOFA score, *the most appropriate organ-dysfunction score to stratify risk in the pediatric sepsis population is yet to estabilish.*

CORE OBJECTIVE OF THE RESEARCH OBJECT

- To progress towards a deeper understanding of the diagnostic, therapeutic and prognostic factors of critically ill children admitted to the PICU with sepsis and septic shock

SUMMARY OF THE PHASES OF THE PROJECT AND SCIENTIFIC ACCOMPLISHMENTS

Phase	Working Package	Timeline	Studies	Scientific Results
1	*Conduction of a systematic review and meta-analysis on vasoactives agent in pediatric fluid-refractory septic shock (FRSS)*	*April 2021 – December 2023*	***1***	**E-poster at the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) Annual Meeting, 15-28 June 2022, Virtual** **Marchetto L**, Zanetto L, Comoretto R, Amigoni A, Daverio M. *Outcomes of pediatric fluid-refractory septic shock according to different inotropic or vasoactive strategies: A systematic review and meta-analysis* **Oral Presentation at the Società di Anestesia e Rianimazione Neonatale e Pediatrica Italiana (SARNEPI) Annual Meeting, 29 September - 1 October 2022, Trieste, Italy** **Marchetto L**, Zanetto L, Padrin D, Comoretto R, Amigoni A, Daverio M. *Outcomes of pediatric fluid-refractory septic shock according to different inotropic or vasoactive strategies: A systematic review and meta-analysis* **The study is being submited for approval for peer-reviewed publication**
2	*Conduction of a retrospective single-center observational study on patients with sepsis admitted to the Pediatric Intensive Care Unit*	*October 2020 – June 2023*	***2***	**Oral presentation at the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) Annual Meeting, 15-28 June 2021, Virtual** **Marchetto L**, Daverio M, Comoretto R, Da Dalt L,

	(PICU)			Wolfler A, Amigoni A. *Comparison of sepsis prognostic scores accuracy in predicting outcomes in critically ill children with sepsis admitted to the PICU: a single tertiary center 10-year experience.* **Winner of Young Investigator Award, 2nd place** **Peer-reviewed publication (see below)** **Marchetto L**, Comoretto R, Gregori D, Da Dalt L, Amigoni A, Daverio M. *Sepsis Prognostic Scores Accuracy in Predicting Adverse Outcomes in Children with Sepsis Admitted to the Pediatric Intensive Care Unit from the Emergency Department: A 10-Year Single-Center Experience. Pediatr Emerg Care. 2023 Jun 1;39(6):378-384*
3	*Creation of a national prospective database on pediatric patients with a diagnosis of infection at admission in the Pediatric Intensive Care Unit (PICU)*	*June 2021 - February 2022*	***3***	**Results presented in November 2023 as a Residency Thesis in Pediatrics** Candidate: Dr. Davide Padrin; Supervisor: Dr.ssa Angela Amigoni; Co-supervisors: Dr. Marco Daverio, Dr. Luca Marchetto *Predictive value of prognostic and diagnostic scores performed in the first 48 hours in critically ill children admitted to PICU with infection:a multi-center cohort prospective study* **The results were sent to the next ESPNIC Annual Meeting in Rome, 2024 in the form of the 3 abstracts (waiting for acceptance)**

4	*Conduction of a multi-center prospective observational study on patients admitted to the Pediatric Intensive Care Unit (PICU) with a diagnosis of infection*	*February 2022 – January 2024*		**Marchetto L**, Comoretto RI, Zoppelletto F, Padrin D, Biban P, Ferrario S, Mondardini MC, Bordin G, Vitale P, Picconi E, Rulli I, Wolfler A, Gregori D, Amigoni A, Daverio M. *Comparison of the Phoenix Sepsis Score with other prognostic scores in a cohort of children with infection admitted to the PICU: a multi-center Italian study* Padrin D, Comoretto RI, Scaravetti S, Di Michele L, Tessari A, Sacco F, Ferrario S, Eusebi G, Bordin G, Vitale P, Picconi E, Rulli I, Wolfler A, Gregori D, Daverio M, **Marchetto L.** *Individual organ dysfunctions in children admitted to the PICU with infection: a multi-center Italian study* Daverio M, Comoretto RI, Alfisi A, Ceschia G, Padrin D, Tessari A, Sacco F, Ferrario S, Caramelli F, Bordin G, Conio A, Picconi E, Rulli I, Wolfler A, Gregori D, Enrico Vidal E, Amigoni, **Marchetto L.** *AKI and RAI score association with clinically significant outcomes in childrenadmitted with infection to the PICU: a multicenter cohort study* **The results will be sent for multiple peer-reviewed publications**

ABSTRACT

Background:

Sepsis and septic shock are leading cause of mortality and morbidity among children globally, thus requiring prompt diagnosis, intervention, and prognostication. From an interventional point of view, the choice of vasoactive agent for fluid-refractory septic shock (FRSS) in pediatric patients remains unclear. Similarly, from a diagnostic and prognostic point of view, the ideal organ-dysfunction score for risk assessment upon admission for pediatric sepsis requires further clarification.

Objectives:

To investigate extensively the diagnostic, therapeutic and prognostic factors of critically ill children admitted to the Pediatric Intensive Care Unit (PICU) with sepsis and septic shock.

Methods:

This is a sequence of three studies:

1. Systematic review and meta-analysis on vasoactive agents in FRSS

2. Single-center retrospective observational cohort study on patients with sepsis admitted to the PICU from January 2010 to December 2019.

3. Multi-center prospective observational cohort study on patients admitted to 8 Italian PICUs with a diagnosis of infection from February 2022 to January 2024 comparing prognostic accuracy of different organ dysfunction scores for sepsis.

Results:

1. Systematic Review: Of the 26,284 identified articles, 13 were included, for a total of 997 children. Twelve studies included 748 patients receiving a single vasoactive agent. Of these, 361 received dopamine, 271 epinephrine, and 116 norepinephrine. Overall pooled mortality for patients receiving a single vasoactive was 12% (95%CI 6-21%) of which 11% (95%CI 3-36%) for patients receiving dopamine, 17% (95%CI 6-37%) for epinephrine, 7% (95%CI 1-48%) for norepinephrine. Four studies reporting data comparing mortality between first-line dopamine (176 patients) and first-line epinephrine (142 patients) tended to favor epinephrine (PR 1.38, 95%CI 0.81-2.38). Regarding the need for MV, the same comparison significantly favored epinephrine (PR 1.12, 95%CI 1.02-1.22).

2. Retrospective Cohort Study: Sixty patients with sepsis were identified, 4 (6.7%) died, 7 (11.7%) developed new disability, 26 (43.3%) experienced prolonged length of stay, 21 (35%) prolonged invasive MV. The prognostic ability in mortality discrimination was significantly higher for organ-dysfunction scores, with PELOD-2 showing the best performance (AUROC 0.924, 95% CI 0.837-1.000), significantly better than SIRS 3/4

criteria (0.924 vs 0.509, p=0.009), SIRS 4/4 criteria (0.924 vs 0.509, p<0.001) and severe sepsis (0.924 vs 0.527, p<0.001).

3. Prospective Cohort Study: Of 466 enrolled patients, 20 died (4.63%). Median duration of mechanical ventilation was 3 days, median PICU LOS was 5 days for the overall sample. Patients meeting the International Pediatric Sepsis Consensus Conference (IPSCC) sepsis criteria had higher mortality (6.61%, *p*=0.027), higher rate of oncologic/hematologic (13.79%, *p*<0.001) and transplant (3.45%, *p*=0.007) comorbidities, longer mechanical ventilation duration (4 days, IQR 2 – 9, *p*=0.003) and PICU LOS (5.5 days, IQR 3 – 11, *p*=0.002). Prediction power for the primary outcome was better than that of the IPSCC criteria (AUROC 0.5774) for pSOFA Schlapbach (AUROC 0.8789, p<0.001), pSOFA Matics (AUROC 0.8855, p<0.001), pSOFA Shime (AUROC 0.9211, p<0.001), P-MODS (AUROC 0.8168, p<0.001) calculated at Day 1, yielding similar results when calculated at Day 2.

Conclusions:

This project highlights and emphasize the need for high-quality data in both interventional and prognostic domains for sepsis. Our systematic review has contributed valuable insights regarding the primary vasoactive agent of choice for patients with FRSS, which presently stands as epinephrine. Regardind the prognostic domains, our retrospective and prospective studies have confirmed a recent body of pediatric and adult evidence supporting the use of organ dysfunction scores for prognostication in infections and sepsis.

PHASE 1

WORKING PACKAGE 1

- **Conduction of a systematic review and meta-analysis on vasoactives agents in pediatric Fluid-Refractory Septic Shock (FRSS)**
- **Timeline: April 2021 – December 2023**

We conducted a systematic review on studies describing outcomes on patients treated with vasoactives in the setting of pediatric FRSS. The aim was to determine the most effective vasoactive in reducing mortality and morbidity in pediatric patients with fluid-refractory septic shock.

Our results showed that, among the patients receiving a single agent, norepinephrine showed the lowest mortality on pooled estimates. The comparison between dopamine and epinephrine favored the latter one on mortality and need for MV. Overall, the study showed heterogenous results, highlighting the need for further RCTs to better delineate the first-line vasoactive agent in children with FRSS.

SCIENTIFIC RESULTS

- **E-poster at the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) Annual Meeting, 15-28 June 2022, Virtual**
    - **Marchetto L**, Zanetto L, Comoretto R, Amigoni A, Daverio M. *Outcomes of pediatric fluid-refractory septic shock according to different inotropic or vasoactive strategies: A systematic review and meta-analysis*
- **Oral Presentation at the Società di Anestesia e Rianimazione Neonatale e Pediatrica Italiana (SARNEPI) Annual Meeting, 29 September - 1 October 2022, Trieste, Italy**
    - **Marchetto L**, Zanetto L, Padrin D, Comoretto R, Amigoni A, Daverio M. *Outcomes of pediatric fluid-refractory septic shock according to different inotropic or vasoactive strategies: A systematic review and meta-analysis*
- **The work was submitted for approval for peer-reviewed publication**

MANUSCRIPT (PHASE 1)

Currently being submitted for approval for peer-reviewed publication

INTRODUCTION

Septic shock is a leading cause of mortality and morbidity among children globally,[1-3] especially in lower-middle (LMIC) or low-income countries (LIC), accounting for 80% of cases and deaths occurring worldwide.[4] Early treatments usually employ fluid resuscitation to maintain adequate organ perfusion.[5] Hemodynamic support using vasoactive agents is a mainstay in the management of patients with Fluid-Refractory Septic Shock (FRSS), but high quality, consistent evidence supporting the appropriate choice of vasoactive agent is limited.

The American College of Critical Care Medicine (ACCM) 2017 guidelines[6] recommend initiation of epinephrine via peripheral access, followed by titration of either central epinephrine or norepinephrine in patients with clinical findings suggestive of cold or warm shock, respectively. The Surviving Sepsis Campaign (SSC) 2020 guidelines[7] recommend either epinephrine or norepinephrine and suggest the use of advanced hemodynamic monitoring to better classify etiology of shock, especially in the face of recent evidence highlighting discordance between clinical assessment and hemodynamic variables measured invasively.[8,9]

Both guidelines present a change from their previous versions,[10,11] where dopamine was recommended as a potential first-line-agent. Dopamine, is now suggested as a second-line agent if both epinephrine or norepinephrine are not available based on increased mortality[12] and occurrence of arrhythmias when compared with norepinephrine in adults.[13] However, two randomized controlled trials (RCTs) investigating the efficacy of dopamine versus epinephrine for the treatment of septic shock in children showed conflicting results.[14,15] A 2020 meta-analysis on three RCTs[14-16] compared dopamine and epinephrine in neonatal and pediatric septic shock and concluded similar efficacy between the two agents.[17]

Furthermore, some authors have advocated combination therapy to allow use of lower doses of medications and mitigation of dose-related side effects. A recent systematic review and network meta-analysis of studies conducted on adult patients[18] investigated the efficacy and safety of multiple vasoactives in reducing 28-days mortality, with the combination of norepinephrine and dobutamine being the most effective. A pediatric RCT published in 2023[19] favored the combination of norepinephrine and dobutamine vs

epinephrine alone in time to shock resolution. The best choice of vasoactive agent(s) in pediatric patients with FRSS remains unclear.

We therefore conducted a systematic review and meta-analysis in children with FRSS to examine the effect of specific vasoactive agents on all-cause mortality and other clinically important outcomes.

METHODS

Study Design

The research question has been illustrated in Population Intervention Comparison Outcomes (PICO) format (*Table S1, Supplemental Digital Content*).

We conducted this systematic review following Cochrane methodology[20] and reported the results according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[21] guideline and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline.[22] We registered the protocol for this systematic review on the International Prospective Register of Systematic Reviews (PROSPERO www.crd.york.ac.uk). This systematic review did not require Institutional Review Board approval.

Inclusion and exclusion criteria

In the absence of a standard definition, we defined FRSS as the persistence of septic shock and poor perfusion despite fluid resuscitation. The inclusion criteria were: a) studies on patients less than or equal to 18 years of age receiving one or two vasoactive agents for FRSS; b) RCTs and observational cohort studies, both prospective and retrospective.

The exclusion criteria were: a) studies on patients receiving three or more vasoactive agents as a first-line therapy or those receiving Extracorporeal Membrane Oxygenation (ECMO) for septic shock, as we considered those cases to be catecholamine-refractory septic shock (CRSS)[23] and not the target for this study; b) non-English language; c) non-peer-reviewed publications, meta-analyses and reviews, editorials, commentaries, abstracts, book chapters, letters, editorials, conference abstracts; d) studies involving only adults or premature neonates; e) studies with less than five patients per vasoactive drug arm to ensure consistency of the treatment provided to the selected cohort of patients; f) studies where neither vasoactive agent specific mortality nor secondary outcomes could not be extracted.

Search Strategy

Three key concepts informed our search strategy: (i) pediatric population, (ii) septic shock, (iii) patients undergoing vasoactive agent treatment. Seven electronic databases

(MEDLINE, EMBASE, Scopus, CINAHL, Web of Science, the Cochrane Library, ClinicalTrials.gov and the ISRCTN registry) were extracted from inception to December 3rd, 2023. Details of the search strategy are reported in *Table S2* (*Supplemental Digital Content*).

Data management & Study Selection

Studies identified from the literature were imported into Rayyan online software[24] for abstract screening, full-text review, and data extraction. The study selection was conducted independently by two investigators both at abstract and full text level. Relevant papers cited in the reference list of the included articles were evaluated and included in the selection if they fulfilled the eligibility criteria. Any disagreement regarding inclusion criteria was resolved by the senior author.

Data Collection

Data extraction included study characteristics, patient demographics, definition of septic shock and FRSS used, type and indications for vasoactive treatment, vasoactive agents received characteristics (i.e., drug, timing of infusion, dosage range, and duration if available), indications for escalation of treatment, adjunctive treatments (mechanical ventilation [MV], steroids, renal replacement therapy [RRT], ECMO), and information about primary and secondary outcomes (see next Section). When the required data were not clearly presented in the study, we contacted the corresponding author. If we could not retrieve the necessary information after this correspondence, we either excluded the article or only used the data presented for clearly specified outcomes.

Outcomes

Our primary outcome was PICU all-cause mortality. Secondary outcomes, if available, included: proportion of patients with shock resolution at a defined time, time to shock resolution, duration of vasoactive support (or vasoactive-free days), need for MV, duration of MV (or ventilation-free days), PICU and hospital length of stay (LOS), organ dysfunction scores at a defined time (or organ-failure free days).

Quality Assessment

Observational cohort studies were analyzed for quality using the Newcastle-Ottawa Quality Assessment scale.[25] RCTs were evaluated using the Revised Cochrane Risk-of-Bias (RoB) tool for randomized trials.[20] Two investigators independently rated each study. Any disagreement between investigators about overall quality assessment was resolved via consensus with a third investigator.

Statistical Analysis

Random effects meta-analysis using generalized linear mixed model was performed to pool outcome proportions for each vasoactive drug considered.[26] Both 95% confidence intervals (CI), with Clopper-Pearson method to stabilize the variance, and 95% prediction intervals were estimated.[27] For studies that compared outcome rates between two vasoactive drugs we computed prevalence ratios (PRs). Pooled PRs were calculated using the inverse variance method. The heterogeneity between study-specific estimates was measured with the I^2 statistics.[28]

We performed subgroup analyses (when at least two studies per subgroup were available) according to study design (RCTs or observational cohort studies) and income level of the country where the studies were conducted (high-income countries [HIC] / upper-middle income countries [UMIC] / LMIC / LIC), according to The World Bank classification.[29] We assessed the publication bias using both the visual inspection of the funnel plot and the Egger test.[30] Sensitivity analyses were performed using the leave-one-out technique to control the between-study heterogeneity[31] and excluding low-quality studies.

Statistical significance was established for outcomes with a p-value <0.05. Data were collected in an Excel database (Microsoft Office 365; Microsoft Corporation, Redmond, WA) and all analyses were performed using the statistical program R (version 4.2.2)[32] with metafor and meta packages.[33] A systematic narrative synthesis was performed to present available data for all studies that could not be included in the meta-analyses.

RESULTS

Study Selection and Characteristics

We identified 26,284 eligible studies through the online database search strategy of which we excluded 10,009 duplicates. Through a manual review of abstract and title, 200 articles were selected for full-text review. Based on the pre-defined inclusion criteria, eight studies were initially included. Data on five more studies were retrieved by direct correspondence with authors. Finally, 13 studies reporting outcomes of different vasoactive agents for FRSS were included, five (38.5%) RCTs, and eight (61.5%) observational cohort studies. The study selection is detailed in *Figure 1*. Among the observational cohort studies, seven (87.5%) were conducted retrospectively, and 11 (84.6%) were single-center. Four (30.8%) studies were performed in HICs, while five (38.4%) and four (30.8%) were performed, in UMICs and LMICs, respectively. Septic shock definition was specified in 10 (76.9%) studies, with the ACCM guidelines[6] reported as the most frequently used document for classification and management (four studies, 30.8%).

Study population

A total of 997 patients with FRSS, aged under 18 years, were included in the pooled study population, of which 748 received a single vasoactive agent (12 studies) and 249 two vasoactive agents (nine studies). Dopamine was the most frequently administered single vasoactive agent (361 patients, 55% of total pooled population), followed by epinephrine (271 patients, 36.2%) and norepinephrine (116 patients, 15.5%). No other agents were used as first-line vasoactive drugs. Among patients who received two vasoactive agents, the combination of dopamine and norepinephrine was the most frequent (74 patients, 29.7% of total pooled population). Drug dosing was reported in 10 studies (76.9%). The specific amount of fluid resuscitation required to define "fluid-refractory" and to trigger the initiation of a vasoactive agent was specified in eight studies (61.5%). Reason for allocation of patients to specific vasoactive strategies was specified in four studies (38.4%). Reason for escalation to a new vasoactive or to more advanced therapies for presumptive CRSS was specified in seven studies (53.8%). A comprehensive description of all the studies reporting outcomes on patients undergoing one or two vasoactive agents is available, in *Table S3* and *Table S4* (*Supplemental Digital Content*), respectively.

Primary outcome

Among patients who were treated with a single vasoactive agent (748 patients, 11 studies), the overall pooled mortality was 12% (95% CI 6-21%). Seven studies explored mortality outcome in patients using dopamine alone[14,15,34-38] and epinephrine alone[14,15,19,36,37,39,40], and five studies consider the use of norepinephrine alone[35,36,39,41,42]. Those who received norepinephrine (116 patients) showed the lowest pooled estimate of mortality (7%, 95% CI 1-48%), with dopamine (361 patients, 11% pooled mortality, 95% CI 3-36%) and epinephrine (271 patients, 17% pooled mortality, 95% CI 6-37%) showing higher pooled mortality (*Figure 2*). For both dopamine and epinephrine pooled mortality estimate, the heterogeneity among studies was high (80-86%).

The comparison of the mortality estimates between patients treated (within the same study) with epinephrine (142 patients) and dopamine (176 patients)[14,15,36,37] showed a tendency towards a higher mortality in the dopamine group (PR 1.38, 95% CI 0.81-2.38), with low level of heterogeneity (*Figure 3*).

Among patients who were administered a two-agent vasoactive strategy (249 patients, nine studies[19,34-36,38,39,41-43]), the overall pooled estimate of mortality was 4% (95% CI 0-29%). Meta-analysis of studies on patients receiving different combination of vasoactive drugs was not performed due to the low number of studies for each drug combination.

Secondary Outcomes

Secondary outcomes were reported inconsistently throughout the studies. The most retrieved secondary outcomes were need for MV[14,15,19,36,37] and hospital LOS,[14,19,35,37,39] reported in five studies (38.4%), while duration of MV,[14,19,35,37] ICU LOS,[14,19,37,39] and duration of vasoactive treatments[19,34,35,39] were reported in four studies each (30.8%) (*Table S4, Supplemental Digital Content*).

Regarding the need for MV, the overall pooled estimate was 73% (95% CI 47-89%) on 420 patients. Patients treated with epinephrine (244 patients)[14,15,36,37] showed the lowest rate of need for MV (64%, 95% CI 32-87%), while those treated with dopamine (176 patients)[14,15,19,36,37,40] reported the highest one (83%, 95% CI 22-99%) (*Figure 4*). No data were available regarding need for MV in those treated with norepinephrine alone.

The comparison of the need for MV between patients treated (within the same study) with epinephrine (142 patients) and dopamine (176 patients)[14,15,36,37] showed a significantly higher pooled prevalence in the dopamine group (PR 1.12, 95% CI 1.02-1.22), without heterogeneity among studies (*Figure 5*).

Meta-analyses on other secondary outcomes were not performed because of low number of studies for each outcome available.

Quality Assessment

As for RCTs, we judged three out of five trials[14,15,19] to be at low RoB according to the Revised Cochrane RoB tool[20] (*Table S6A*, *Supplemental Digital Content*). All but one[34] of the observational cohort studies showed fair or high quality (score > 5/9) on each assessment area (selection, comparability, outcome) according to the Newcastle-Ottawa Scale (NOS)[25] (*Table S6B*, *Supplemental Digital Content*).

Subgroup Analyses

Subgroup analyses (*Figures S6*, *Supplemental Digital Content*) were performed on those studies reporting outcomes related to the exposure to a single vasoactive agent.

Subgroup analysis for HIC vs UMIC/LMIC was performed only on those studies reporting outcomes for patient undergoing dopamine as a single vasoactive agent. Pooled-mortality among UMIC/LMIC[14,15,37,38] (27%, 95% CI 9-59%) was higher compared to studies from HIC[34-36] (3%, 95% CI 0-28%) (*Figure S6.1, Supplemental Digital Content*).

Subgroup analysis according to the design of the study (RCTs vs observational cohort studies) was performed on mortality prevalence rate according to single vasoactive agent exposure. Both epinephrine and dopamine showed higher pooled-mortality in RCTs

compared to observational cohort studies and the overall sample. Dopamine pooled-mortality in RCTs[14,15,36] was 19% (95% CI 0-96%) compared to 8% (95% CI 1-36%) in observational cohort studies[34,35,37,38] and 11% (95% CI 3-36%) in the overall sample. Epinephrine pooled-mortality in RCTs[14,15,19,36,40] was 24% (95% CI 9-51%), compared to 7% (95% CI 0-95%) in observational cohort studies[37,39] and 17% (95% CI 6-37%) in the overall sample (*Figure S6.3-S6.4, Supplemental Digital Content*).

Publication Bias Assessment and Sensitivity Analyses

No publication bias was seen after inspection of the funnel plot and the Egger test (*Figure S7.1-S7.5, Supplemental Digital Content*).

We performed leave-one-out sensitivity analysis for both outcomes (mortality and need for MV), which overall confirmed our main results (*Figure S7.6-S7.12, Supplemental Digital Content)*. Furthermore, a second sensitivity analysis was performed by excluding low-quality studies[34,36,40] (*Figure S7.13-S7.16 Supplemental Digital Content*). The exclusion of low-quality studies led to a higher prevalence of mortality in patients who received only dopamine (20%, 95% CI 7-49% vs 20%, 11% CI 3-36%) and an overall slightly higher prevalence of need for MV (80%, 95% CI 50-94% vs 73%, 11% CI 47-89%).

DISCUSSION

This systematic review and meta-analysis of 13 studies including 997 patients compared different first-line vasoactive agent strategies for the treatment of FRSS in children. Among single vasoactive strategies, norepinephrine was associated with the lowest mortality rate, followed by dopamine and epinephrine. The overall pooled estimate of mortality rate was lower in patients treated with two vasoactive agents when compared to those receiving only one vasoactive agent. The comparison between epinephrine and dopamine, available in four studies, showed a tendency toward better survival for epinephrine, but this result was not statistically significant. Exploring the need for MV as a secondary outcome, we found the highest pooled estimate for patients treated with dopamine. The comparison between epinephrine and dopamine, available in four studies, significantly favored epinephrine as vasoactive agent.

Importantly, recent guidelines on this topic by ACCM[6] and SSC,[7] have reshaped the approach to the selection of the first vasoactive agent to be used. Dopamine is now considered a second-line choice, with the decision between epinephrine and norepinephrine guided by the patient's clinical condition and advanced hemodynamic monitoring. These recommendations align with the findings of our review where patients treated with norepinephrine as first choice demonstrated the highest survival and patients receiving epinephrine showed a tendency to better survival and a lower need for MV compared to

dopamine. Interestingly, all the high-quality evidence supporting these conclusions come from UMIC and LMICs,[14,15] where, according to our subgroup analysis comparing HIC vs UMIC/LMICs countries, the pooled mortality of dopamine was the highest.

Historically, the choice of vasoactive agents in pediatric FRSS has leaned towards those with inotropic properties (e.g., dopamine and epinephrine), primarily due to the relatively higher incidence of septic myocardial dysfunction in the pediatric population as compared to adults.[44,45] Epinephrine is a potent inotropic and peripheral vasoconstrictor agent at high doses, while dopamine, in contrast, has a lower inotropic effect. Both agents are known for exacerbating tachycardia, arrhythmias and increasing myocardial oxygen consumption.[46,47] Among known dopamine's side effects, the unpredictable response to drug dosing is also reported, especially in infants and young children: in those subjects, dopamine's insensitivity and depletion of body catecholamines during shock have been described.[48,49] This last factor and the lower overall inotropism may explain why epinephrine appears to be a more consistent and favourable choice than dopamine in the management of pediatric FRSS.

On the other hand, norepinephrine is known for increased vasoconstriction, mild chronotropy and modest inotropic effect. Norepinephrine is the vasoactive agent of first choice in septic shock in adults,[50] while it is recommended only for children with "warm" shock at presentation, according to the current ACCM guidelines.[6] However, it is used as first-line agent by many pediatric intensivists in Europe.[51] In our study, use of norepinephrine was associated with the lowest mortality rate, and could potentially be considered as the first-line vasoactive of choice in patients with undifferentiated shock, especially because of its properties of improved ventriculo-arterial coupling, increased coronary artery perfusion and modest inotropy.[52]

Among included studies, a recent RCT by Banothu et al.[19] compared the combination of norepinephrine and dobutamine with epinephrine alone as first-line treatment for patients presenting with "cold" shock. This particular study yielded promising results, favouring the combination of vasoactive drugs in time to shock resolution. In our review we observed that pooled mortality of patients receiving two vasoactive agents was lower compared to those receiving only one drug.

Notably, our review revealed a significant heterogeneity on the definition, management, and treatment of FRSS (*Table S3 and Table S4*). Additionally, we observed differences in measures used across studies to assess the improvement of FRSS. These variations ranged from overall shock resolution to time-to-shock resolution, organ dysfunction scores, liberation from organ support (*Table S5*), leading to high levels of

statistical heterogeneity among studies. Furthermore, these findings highlight the need for an effort to improve definitions and standardize the management of FRSS worldwide.

To the best of our knowledge, this is the first systematic review evaluating the efficacy of all the possible first-line vasoactive agents for pediatric patients with FRSS. Our review significantly contributes to the existing literature by offering a more extensive body of evidence, adding important considerations in the management of vasoactive agents for pediatric FRSS.

Our study does have several limitations that need to be acknowledged. We observed considerable heterogeneity among the included studies, which could lead to reduced representativeness of the pooled estimates. In addition, it is well-established that the incidence and mortality rates for septic shock are higher in LMICs and LICs.[4] Moreover, the absence of randomized data from HICs, and the lack of information regarding the severity of patients' conditions at baseline, are two important issues decreasing the generalizability of our results. However, despite these limitations, we think the findings of this systematic review could provide valuable insights on the choice of first-line vasoactive agents in the management of pediatric FRSS pending more definitive RCTs.

CONCLUSIONS

Norepinephrine showed the lowest pooled mortality rate in pediatric patients presenting with FRSS and could potentially be considered the first-line vasoactive for patients with undefined shock, especially in combination with another inotropic agent. Epinephrine significantly reduced the need for MV and showed a lower mortality when compared to dopamine. Further RCTs and high-quality data are required to evaluate efficacy and safety of first-line vasoactive agents in pediatric FRSS.

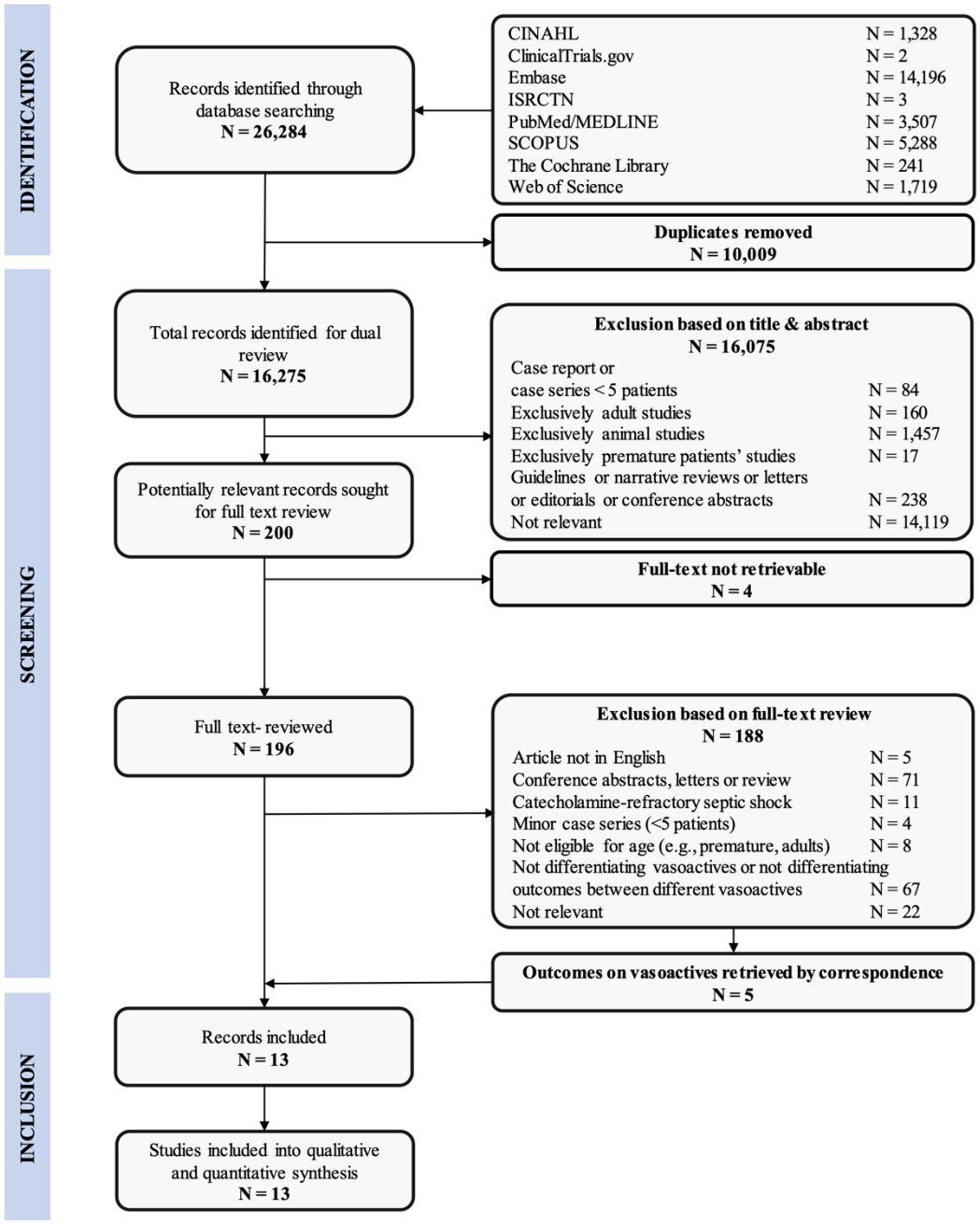


Figure 1. Flow-diagram of the studies selection process

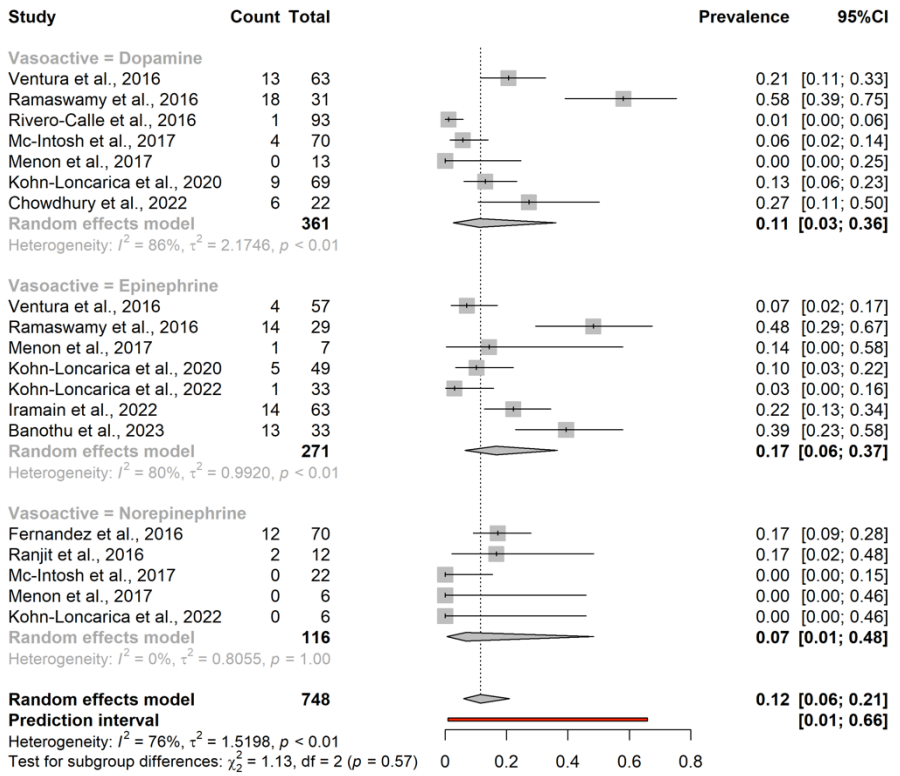


Figure 2. Forest-plot of pooled-estimate for mortality in patients undergoing a single vasoactive as first-line agent

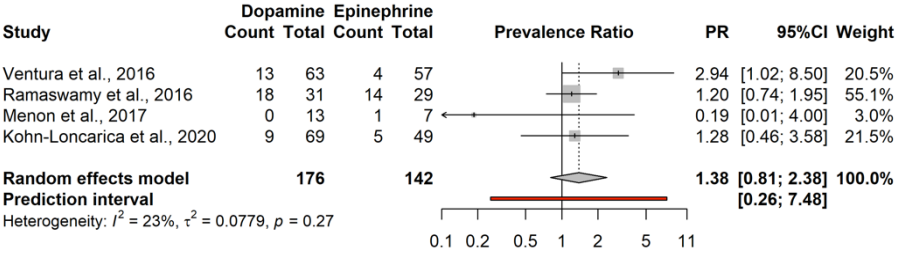


Figure 3. Forest-plot of pooled-estimate for mortality comparing patients undergoing dopamine vs epinephrine as first-line vasoactive agent

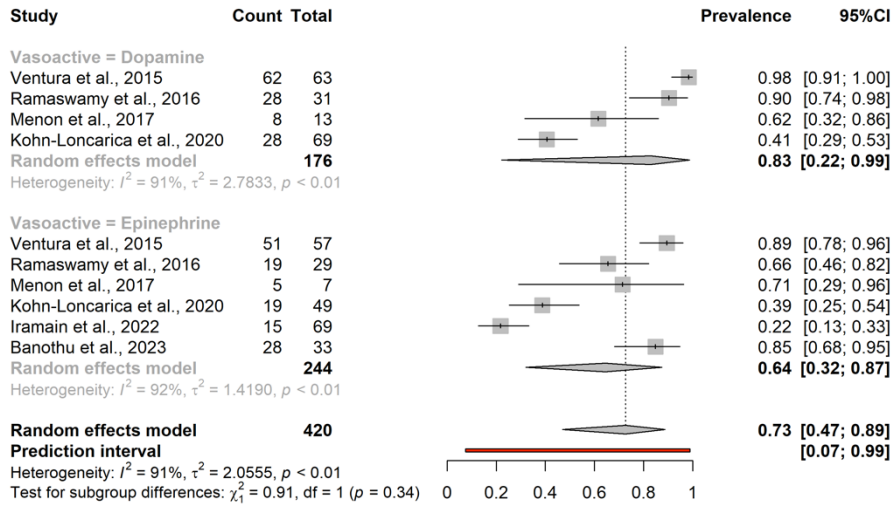


Figure 4. Forest-plot of pooled-need for MV in patients undergoing a single vasoactive as first-line agent

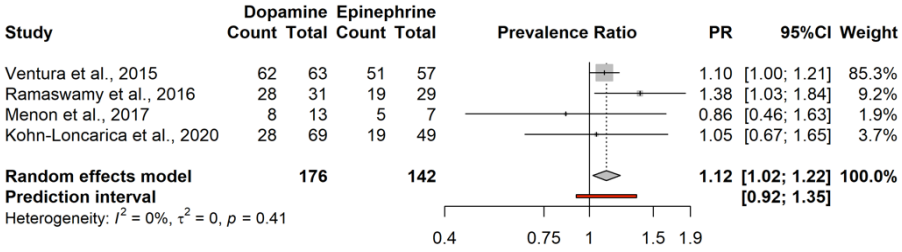


Figure 5. Forest-plot of pooled-estimate for need for MV comparing patients undergoing dopamine vs epinephrine as first-line vasoactive agent

PHASE 2

WORKING PACKAGE 2

- **Conduction of a retrospective single-center observational study on patients with sepsis admitted to the PICU**
- **Timeline: October 2020 - June 2023**

We conducted a retrospective study on patients with sepsis admitted to the PICU from the Pediatric Emergency Department (PED) in our Institution from the year 2010 to the year 2019. The aim was to compare the performance of several prognostic scores calculated in the first 24-hour of admission ("Day-1") in predicting outcomes of critically ill children admitted with sepsis to the PICU.

We hypothesized that organ-dysfunction scores performed better in predicting relevant outcomes compared to IPSCC-based scores (i.e., SIRS criteria, severe sepsis criteria). Our results confirmed those primary hypotheses, showing that organ dysfunction scores calculated in the first 24 hours had better performances in predicting both mortality and morbidity (i.e., prolonged LOS, prolonged MV, new disability), compared to IPSCC-based scores (see Manuscript).

SCIENTIFIC RESULTS

- **Oral presentation at the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) Annual Meeting, 15-28 June 2021, Virtual**
    - **Marchetto L**, Daverio M, Comoretto R, Da Dalt L, Wolfler A, Amigoni A. *Comparison of sepsis prognostic scores accuracy in predicting outcomes in critically ill children with sepsis admitted to the PICU: a single tertiary center 10-year experience.*
    - **Winner of Young Investigator Award, 2nd place**
- **Peer-reviewed publication (see below)**
    - **Marchetto L**, Comoretto R, Gregori D, Da Dalt L, Amigoni A, Daverio M. *Sepsis Prognostic Scores Accuracy in Predicting Adverse Outcomes in Children with Sepsis Admitted to the Pediatric Intensive Care Unit from the Emergency Department: A 10-Year Single-Center Experience. Pediatr Emerg Care. 2023 Jun 1;39(6):378-384.*

MANUSCRIPT (PHASE 2)

Published in June 2023

Marchetto L, Comoretto R, Gregori D, Da Dalt L, Amigoni A, Daverio M.

Sepsis Prognostic Scores Accuracy in Predicting Adverse Outcomes in Children with Sepsis Admitted to the Pediatric Intensive Care Unit from the Emergency Department: A 10-Year Single-Center Experience. Pediatr Emerg Care. 2023 Jun 1;39(6):378-384.

BACKGROUND:

Sepsis and septic shock are leading cause of morbidity and mortality for infants and children worldwide[1-3]. Recognition and prognostication of sepsis presents specific challenges in the pediatric population: pediatric sepsis may have a particularly fulminant course, with the majority of deaths happening during the first 24 hours from referral, with a large percentage of them not even being able to receive Pediatric Intensive Care Unit (PICU) level-of-care [53]; the cornerstone of the pediatric sepsis definition, proposed in 2005 during the International Pediatric Sepsis Consensus Conference (IPSCC)[54], is still represented by the Systemic Inflammatory Response Syndrome (SIRS) criteria. Those criteria encompass nonspecific adaptative mechanisms (e.g., tachycardia, tachypnea) that are commonly seen in almost every febrile child presenting to the Pediatric Emergency Department (PED) [55].

In the last two decades, the validity of SIRS criteria to identify and risk-stratify patients with sepsis has been especially questioned in the adult population, where they demonstrated insufficient sensitivity and specificity [56,57]. Accordingly, a SCCM/ESICM joint task force has recently produced a new consensus for adults, named Sepsis-3 [58], which replaced the SIRS criteria and the term severe sepsis with the more specific definition of sepsis as a "life-threatening organ dysfunction" syndrome [58]. The Sequential Organ Failure Assessment (SOFA) score was selected by the task force to quantify the degree of organ dysfunction, and it has shown to have a good performance in discriminating mortality among large cohort of adult patients with sepsis [59].

Unfortunately, the task force excluded the pediatric population from the development and validation of this new definition, acknowledging that the new criteria are not designed for children and that future studies should consider age-specific physiology and risk stratification. As such, significant effort has recently been made by several authors to identify and validate a quality organ dysfunction score for pediatric sepsis [60-62]. Three types of age-adapted pediatric SOFA (pSOFA) score have subsequently been proposed in

pediatrics [60,61,63], two of which showing promising results on their prognostic prediction accuracy on mortality after undergoing a first internal validation. Another organ-dysfunction score, the PEdiatric Logistic Organ Dysfunction score-2 (PELOD-2) [64], developed for pediatric patients admitted to the ICU, has also been tested in the pediatric sepsis population showing good prognostic accuracy [61,65]. Efforts were also made to produce "quick" scores, with the creation of a pediatric quick SOFA (qSOFA) score [61] and a pediatric quick PELOD-2 (qPELOD-2) score [65], however generally resulting with inferior accuracy [61,66,67]. Those studies present some limitations: first, no study has ever compared all the prognostic scores available in the literature. Second, these studies considered only the ICU hospitalization to calculate the prognostic scores, without considering the time spent by the patient prior to ICU admission (e.g., the PED, where the patients present and could be potentially more sick). Finally, no study compared different organ-dysfunction scores in predicting potential morbidity for the patient rather than just mortality.

Therefore, the aim of our study was to compare the performance of several prognostic scores calculated in the first 24 hours of admission in predicting both mortality and morbidity outcomes (e.g., functional outcomes) among critically ill children presenting to the PED and then admitted to the PICU with a diagnosis of sepsis. We hypothesized that scores which quantify the presence of organ dysfunction would better identify patients at higher risk of mortality and morbidity compared to 2005 IPSCC criteria.

METHODS:

Study population, design and setting

We performed a single-center, retrospective cohort study of patients < 18 years who presented to the PED and were subsequently admitted to the PICU with a diagnosis of sepsis from January 1st, 2010 to December 31st, 2019. Both units are part of an academic, multi-disciplinary tertiary level pediatric hospital in Padova, Italy. Patients were considered eligible if presenting criteria of sepsis according to the IPSCC guidelines[54] (see ***Figure e1***, ***Appendix 2*** for IPSCC definitions) within the first 24 hours of admission from the PED. Each hospitalization with a PICU admission of the same patient was treated independently.

Data collection

Data on demographics, vital signs, clinical examination and laboratory investigations were extracted from the Electronic Medical Record of the hospital. Information about medical treatment, duration of mechanical ventilation (MV), PICU and hospital length of stay (LOS), mortality, Pediatric Overall Performance Category (POPC) score at the admission and discharge from PICU were collected from the TIPNET (Terapie Intensive Pediatriche NETwork) database, a large multi-center prospective registry of PICU patients in

Italy created in 2010 including all the patients treated at our PICU. In particular, in our Institution, patients are entered into the database by the discharging staff physician at the time of patient's transfer.

As abovementioned, children with sepsis were diagnosed according to the criteria of SIRS, sepsis, severe sepsis, and septic shock by the ICCPPS [54]. For each patient, we calculated 8 prognostic scores in the first 24 hours of hospitalization (including the time of the patient's management in the ED), namely "day-1". The most abnormal value of each variable observed during the considered period span was used to calculate the scores. We calculated scores derived from the IPSCC guidelines (day-1 SIRS 3 criteria [54], day-1 SIRS 4 criteria [54], day-1 severe sepsis [54]), multiple pediatric-adapted organ-dysfunction scores (day-1 pSOFA Matics' version [60], day-1 pSOFA Schlapbach's version [61], day-1 pSOFA Shime's version [63], day-1 PELOD-2 [64], day-1 P-MODS [68]) and their correspondent quick versions (day-1 qSOFA [61], day-1 qSOFA-L [67], day-1 qPELOD-2 [65]) (see ***Appendix 2*** for scores definitions).

Patients' outcomes and outcome measures

The primary outcome of the study was mortality. As secondary outcome we considered a composite outcome ("poor outcome") of death or new disability at PICU discharge. We defined "new disability" as a change from the baseline POPC score of the patient at admission at the PICU by greater than or equal to 1 category [69]. The POPC score ranges from 1 to 6 with score of 1 assigned to "no disability" and score of 6 to death or brain death (see ***Appendix 2***) [70]. Other secondary outcomes were prolonged PICU LOS (defined as a LOS longer than 5 days) and prolonged duration of invasive MV (defined as a duration of more than 3 days).

Statistical Analysis

We used a convenience sample based on the number of patients with sepsis admitted to the PICU from the PED from January 1st, 2010 to December 31st, 2019. The descriptive analysis of the sample is reported using the median and the interquartile range (IQR) (I-III quartile) for continuous variables and absolute numbers and relative percentages for categorical ones. The performance of each score to discriminate the primary outcome (mortality at PICU discharge) or the secondary outcomes (death or new disability, prolonged PICU LOS, prolonged duration of invasive MV) was evaluated using the area under the receiver operating characteristics curve (AUROC). Comparison between AUROC was performed using the DeLong method [71]. The statistical significance was set at a p value < 0.05. The analyses were performed by a statistician using the statistical program R (version 4.1.1) with *pROC* package [72].

Ethical aspects

The present research study was conducted in compliance to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement on observational studies [73]. Due to the retrospective nature of the study in the absence of sensible the Ethics Committee approved the study and decided for a waiver of consent.

RESULTS:

Study population

During the study period, 4,394 patients were admitted to the PICU, of which 366 patients (8.3%) were admitted from the PED. Among them, 99 patients were admitted for a suspected infection (27.0%) and 60 patients (16.4%) were included in the final analysis fulfilling the IPSCC criteria for sepsis. See ***Figure 1*** for a schematic depiction of patients screening and enrollment.

Table 1 reports the baseline characteristics, prognostic factors and outcomes of the patients included. Of 60 patients, 53.3% were boys. Median age was 27 months (IQR 6 – 78.5). Most of the patients were Caucasian (71.7%) and 58.3% of them suffered from at least one comorbidity. Mean predicted mortality with PIM-3 [74] at admission was 6%. At admission, 43 (71.7%) patients presented with a "favorable" POPC (i.e., POPC ≤ 2, good overall performance or minor disability), while 17 patients (28.3%) presented with "unfavorable" POPC (i.e., POPC > 2, moderate or severe disability). Four patients (6.7%) died while admitted in PICU, 11 patients (18.3%) presented with "poor outcome" (see above, death or new disability at discharge). Three patients (5.0%) presented a new "mild" disability, 2 patients (3.3%) presented a new "moderate" disability, 2 patients (3.3%) presented a "new" severe disability. No patient was discharged in coma/vegetative state. Thirty-four patients (56.7%) required invasive MV. Median duration of invasive MV was 99 hours (IQR 32 – 222). Nineteen patients (31.7%) required vasopressors in the first 48 hours of hospitalization. Median PICU LOS was 3.5 days (IQR 1 – 13.2). Twenty-six patients (43.3%) experienced prolonged PICU LOS. Median hospital LOS was 14 days (IQR 9 – 25).

IPSCC definitions

Among the 60 patients included in the study, 31 presented with 2 SIRS criteria, 16 patients with 3 criteria, and 13 patients with all 4 criteria (see ***Figure 2A***). Two patients (3.3%) met criteria for sepsis, 58 (96.7%) for severe sepsis, and among them 31 (51.7%) for septic shock (see ***Figure 2B***)

Performance of the scores for the primary outcome

Table 2 reports the performance of the sepsis scores in predicting our outcome measures expressed as the AUROC of the scores. PELOD-2 resulted in the highest performance among the scores (AUROC 0.924, 95% CI 0.837-1.000) and was used as a reference.

Performance of PELOD-2 resulted significantly higher compared to SIRS 3 criteria (0.924 vs 0.509, $p = 0.009$), SIRS 4 criteria (0.924 vs 0.509, $p < 0.001$) and severe sepsis (0.924 vs 0.527, $p < 0.0001$) at discriminating mortality. The others organ-dysfunction scores (qSOFA, Matics' pSOFAs, Shime's pSOFA, qPELOD-2) resulted in lower AUROC compared to PELOD-2 but without statistical significance. ***Figure 3*** shows all the scores' AUROC in predicting mortality. ***Figure 3D*** illustrates the accuracy of PELOD-2 in predicting mortality for different score cut-off (from 7 to 11). The best binary performance for PELOD-2 at discriminating mortality was met at cut-off of PELOD-2 > 10, with an AUROC 0.902 (95% CI 0.849-0.954).

Also, qSOFA, qSOFA-L, Schlapbach's pSOFA, Shime's pSOFA, qPELOD-2, resulted all significantly better than SIRS 3, SIRS 4 criteria and sepsis criteria **(**see ***Table e10***, ***Appendix 2*****)** in discriminating mortality. Matics' pSOFA and P-MODS performance resulted significantly better than severe sepsis and SIRS 4 criteria, trending to be better than SIRS 3 criteria, while without statistical significance.

Performance of the scores for the secondary outcomes

Among the scores, PELOD-2 resulted to have the best performance in predicting a "poor outcome" (AUROC 0.762, 95% CI 0.584-0.939). PELOD-2 resulted significantly better than severe sepsis (0.762 vs 0.525, $p < 0.023$), and trending to be better than SIRS 3 criteria and SIRS 4 criteria but without statistical significance (see ***Table 2***).

Finally, PELOD-2 was the only prognostic score resulting in a significantly better performance than IPSCC criteria at discriminating a prolonged MV (AUROC 0.750, 95% CI 0.628 – 0.871). PELOD-2 trended to have a higher performance also at discriminating a prolonged PICU LOS (AUROC 0.684, 95% CI 0.549-0.819). The performance of other scores seemed to be similar to each other (see ***Table e11-S13***, ***Appendix 2*** for more specific on Secondary Outcomes).

DISCUSSION:

This retrospective single-center cohort study of 60 children with sepsis admitted to the PICU from the PED assessed the accuracy of several prognostic scores calculated in the first 24 hours from admission in predicting mortality and morbidity at PICU discharge. A better performance of organ dysfunction scores in predicting death compared to IPSCC-

derived criteria (i.e., SIRS criteria and severe sepsis criteria) has been observed. Among the organ dysfunction scores, PELOD-2 presented the best performance measures, resulting significantly more accurate than the IPSCC-derived criteria in discriminating both the primary and some secondary outcomes.

The validity of IPSCC-derived criteria (especially SIRS criteria) to evaluate severity of patients has already been questioned in the last two decades in the adult population, resulting in a paradigmatic change during last Sepsis-3 Consensus Statement [58]. As mentioned before, the consensus resulted in the elimination of the definitions of SIRS and severe sepsis, underlining that sepsis is already differentiated from uncomplicated infection by the presence of a life-threatening organ dysfunction. The operationalization of clinical criteria to identify individuals meeting outcomes consistent with sepsis has conducted to the implementation of the SOFA score. This instrument, validated using big but limited-to-adult datasets [59], is now considered the gold standard to prognosticate mortality in adult patients with suspected infection.

Recently, several authors compared the performance of pediatric adapted organ-dysfunction scores (i.e., pSOFA, PELOD-2) as outcome predictors in large cohort of critically ill children, resulting in excellent performance of organ dysfunction score in predicting mortality and other relevant outcomes [61,65]. Our study confirms these recent new evidences. In our study, we did not find any clear statistical superiority of an organ-dysfunction score compared to the others, probably secondary to the small dimension of the sample size. However, as already stated, PELOD-2 demonstrated the highest performance at discriminating mortality, supporting findings of other studies [65], and suggesting its promising use to standardize definitions and diagnostic criteria for pediatric sepsis.

A limitation of previous studies is that they did not evaluate the prognostic accuracy of organ-dysfunction scores in any functional outcome of the patients. These outcomes are becoming the reference points in the short and long-term evaluation of patients after PICU admission, especially considering recent improvements on sepsis mortality rate over the last two decades [1]. The POPC [70] is a qualitative tool validated for assessing functional morbidity in large cohorts of critically-ill children [75,76]. In multiple retrospective studies by Typpo and colleagues [77,78], the presence of day-1 multiple organ dysfunction (at the time quantified trough IPSCC criteria) was significantly associated with death or change in POPC score greater than 3 points compared to baseline. In our cohort, about half of the patients had at least mild disability at PICU admission, which is in agreement with data reported by other authors on previous large cohort studies [78,79]. At PICU discharge, 12% of the patients presented a new disability, while 18.3% of the patients had a “poor outcome”, i.e. a composite outcome of mortality and new disability [69]. PELOD-2 resulted as the organ-

dysfunction score showing the best performance in predicting a "poor outcome", although being significantly higher only compared to severe sepsis score. These preliminary results need to be replicated in larger populations.

Interestingly, almost 97% of our patients resulted classified as "severe sepsis" by IPSCC criteria. This data suggests a high severity of the patients in our cohort, likely reflecting a high institutional threshold for admitting patients in the PICU from the PED. This is consistent with a median PELOD-2 score of 7 (IQR 6.0 – 11.0) which is higher compared to ones reported in other previous cohorts [65]. We consider that a limitation, as probably a percentage of septic patients with more favorable outcomes were managed outside the PICU, limiting the variability and the dimension of the sample included in our study.

Overall, these findings support a trend of recent evidence in the pediatric critical care community that suggests a central role for organ-dysfunction scores to help standardize prognostication in pediatric sepsis. In particular, this study is among the first ones that showed a better prognostic accuracy of organ-dysfunction scores in predicting mortality and with promising results also on predicting the morbidity (e.g., new disability) of patients with sepsis.

The present study presents several limitations. First, the results were generated using retrospective data from a single center. However, most of the outcome data were retrieved from a prospective compiled registry, limiting the number of missing data in the sample. Second, we did not consider a comprehensive cohort of patients with infection but only patients with a confirmed diagnosis of sepsis, according to IPSCC criteria, limiting our chance to make assumption on the performance of IPSCC criteria from a diagnostic standpoint. Third, only patients admitted from the PED have been assessed and only the first 24 hours of hospitalization of the patient (comprehensive of the time in the PED) have been considered for the analysis. This limited the study sample to subjects with community-acquired infections and our prognostic considerations to this particular timespan of patients' care. However, this aspect could be considered also a point of strength, as the aim was to evaluate the prognostic accuracy of multiple tools in patients with sepsis within the first hours of hospital admission. Fourth, due to the retrospective nature of the study, a convenience sample has been used limiting the statistical power of the study. Consequently, the relatively small sample size might have hindered the analysis, in particular resulting in a less precise estimation of the accuracy of the scores. These limitations reduce the generalization of the present findings highlighting the need for future prospective, multicenter, larger studies to draw firmer conclusions.

CONCLUSIONS:

In conclusion, IPSCC-derived criteria during the first 24 hours of admission had poor performance to discriminate children with sepsis at higher risk for mortality and poor functional outcomes. At the opposite, organ dysfunction scores seemed to perform better in discriminating mortality at PICU discharge and trended to be better in evaluating functional outcomes. In particular, the PELOD-2 score showed the best performance among several organ dysfunction scores considered. Further studies in larger cohorts are needed to confirm these results.

Characteristic	Sample N=60
Age (months), median (IQR)	27.0 (6.0 – 78.5)
Male, No. (%)	32 (53.3%)
Ethnicity, No (%) African Arabian or Asian Caucasian Hispanic or Latino Mixed	 10 (16.7%) 3 (5.0%) 43 (71.7%) 1 (1.7%) 3 (5.0%)
Comorbidities, No (%) None Cardiologic Gastroenterological Metabolic Neurologic/neuromuscular Oncohematologic Prematurity Renal Respiratory Syndromic/malformative Other	 25 (41.7%) 3 (5.0%) 1 (1.7%) 1 (1.7%) 15 (25.0%) 3 (5.0%) 12 (20.0%) 5 (8.3%) 5 (8.3%) 2 (3.3%) 1 (1.7%)
POPC score POPC score at admission, median (IQR) Unfavorable POPC at admission (>2), No (%) POPC score at discharge, median (IQR)	 1 (1 – 3) 17 (28.3%) 2 (1 – 4)
Need for MV, No (%)	34 (56.7%)
Required inotropic-vasoactive infusion, No (%)	19 (31.6%)
PIM-3 score (predicted death rate), median percentage (IQR)	6 (1 – 14)
Prognostic scores, median (IQR) qSOFA qSOFA-L pSOFA (*Schlapbach)* pSOFA (*Matics PaO_2 version*) pSOFA (*Matics SpO_2 version*) pSOFA (*Shime version*) qPELOD-2 PELOD-2 P-MODS	 2.0 (2.0 – 3.0) 2.5 (2.0 – 3.0) 7.5 (5.0 – 9.0) 7.5 (5.0 – 10.0) 7.0 (5.0 – 10.0) 6.5 (5.0 – 9.2) 1.0 (1.0 – 1.0) 7.0 (4.0 – 9.2) 3.0 (1.0 – 4.0)
Outcomes Death, No (%) New disability, No (%) Duration of invasive MV (hours), median (IQR) PICU LOS (days), median (IQR)	 4 (6.7%) 7 (11.7%) 99 (32 – 222) 3.5 (1.0 – 13.2)
IQR: Interquartile Range MV: Mechanical ventilation PICU: Pediatric Intensive Care Unit LOS: Length of Stay	

Table 1. Baseline characteristics, prognostic factors and outcomes of the sample

Table 2. Comparison of PELOD-2 with SIRS criteria, severe sepsis, qSOFA, qSOFA-L, pSOFA (Schlapbach version), pSOFA (Matics PaO_2 version), pSOFA (Matics SpO_2 version), pSOFA (Shime version), qPELOD-2 and P-MODS at discriminating primary and secondary outcomes

	Primary outcome: Mortality		**Secondary outcome: ΔPOPC ≥ 1 or death**		**Secondary outcome: PICU LOS > 5 days**		**Secondary outcome: Duration of invasive MV > 3 days**	
Scoring system	**AUC (95% CI)**	***P* value for AUC comparison**	**AUC (95% CI)**	***P* value for AUC comparison**	**AUC (95% CI)**	***P* value for AUC comparison**	**AUC (95% CI)**	***P* value for AUC comparison**
PELOD-2	0.924 (0.837-1.000)	.	0.762 (0.584-0.939)	.	0.684 (0.549-0.819)	.	0.750 (0.628-0.871)	.
SIRS 3 criteria	0.509 (0.218-0.799)	0.009	0.594 (0.429-0.759)	0.177	0.537 (0.407-0.667)	0.127	0.506 (0.370-0.641)	0.010
SIRS 4 criteria	0.616 (0.560-0.672)	< 0.001	0.633 (0.570-0.695)	0.183	0.514 (0.408-0.621)	0.056	0.517 (0.403-0.630)	0.007
Severe sepsis	0.527 (0.497-0.557)	< 0.001	0.525 (0.432-0.618)	0.023	0.543 (0.496-0.590)	0.057	0.539 (0.496-0.581)	0.002
qSOFA	0.866 (0.808-0.925)	0.281	0.733 (0.595-0.870)	0.802	0.662 (0.539-0.786)	0.816	0.634 (0.505-0.764)	0.205
qSOFA-L	0.880 (0.754-1.000)	0.568	0.724 (0.557-0.890)	0.760	0.626 (0.493-0.759)	0.547	0.630 (0.491-0.769)	0.207
pSOFA (*Schlapbach)*	0.929 (0.812-1.000)	0.952	0.710 (0.512-0.910)	0.702	0.633 (0.493-0.773)	0.609	0.610 (0.468-0.751)	0.145
pSOFA (*Matics PaO_2 version*)	0.855 (0.657-1.000)	0.533	0.707 (0.533-0.881)	0.666	0.593 (0.448-0.738)	0.369	0.590 (0.446-0.734)	0.099
pSOFA (*Matics SpO_2 version*)	0.830 (0.588-1.000)	0.478	0.704 (0.531-0.877)	0.649	0.608 (0.464-0.752)	0.451	0.593 (0.450-0.736)	0.104
SOFA (*Shime version*)	0.882 (0.727-1.000)	0.641	0.742 (0.564-0.920)	0.879	0.623 (0.481-0.765)	0.541	0.597 (0.453-0.740)	0.113
qPELOD-2	0.830 (0.763-0.898)	0.098	0.748 (0.611-0.885)	0.903	0.573 (0.449-0.697)	0.238	0.616 (0.493-0.739)	0.133
P-MODS	0.862 (0.654-1.000)	0.588	0.653 (0.418-0.888)	0.471	0.565 (0.415-0.715)	0.250	0.597 (0.446-0.748)	0.126

AUC: Area under the ROC Curve
PICU: Pediatric Intensive Care Unit
LOS: Length of Stay
MV: Mechanical ventilation

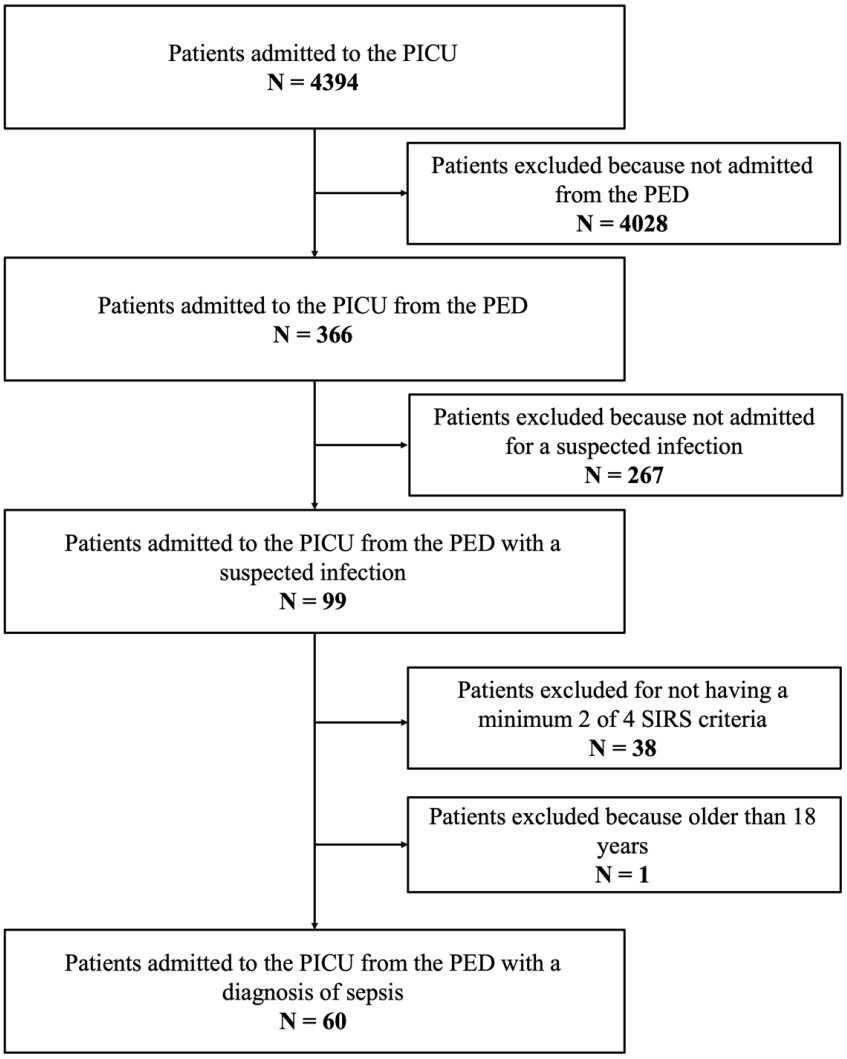
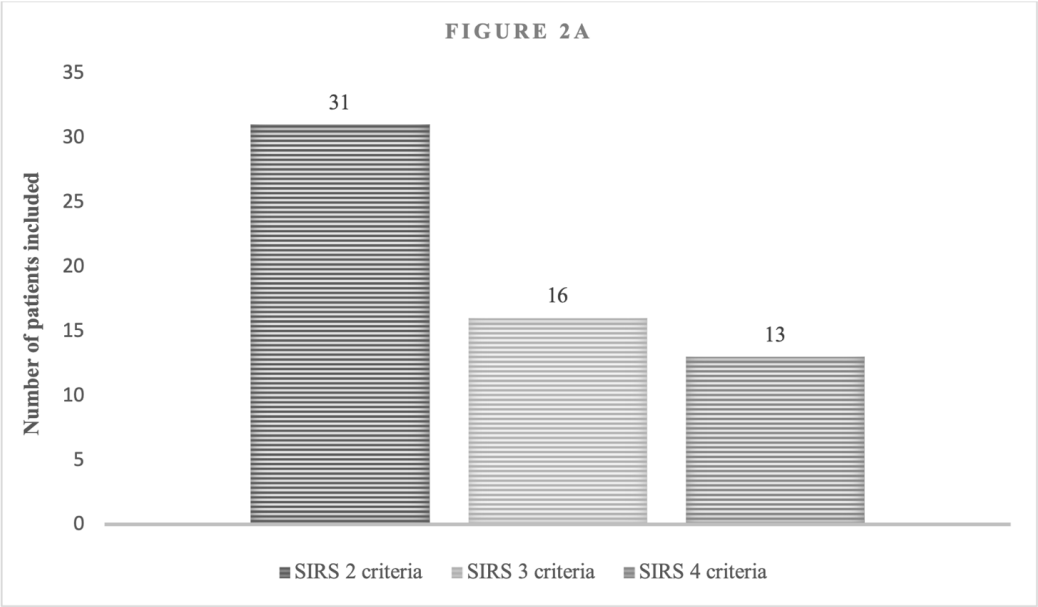


Figure 1. Schematic depiction of patients screening and enrollment



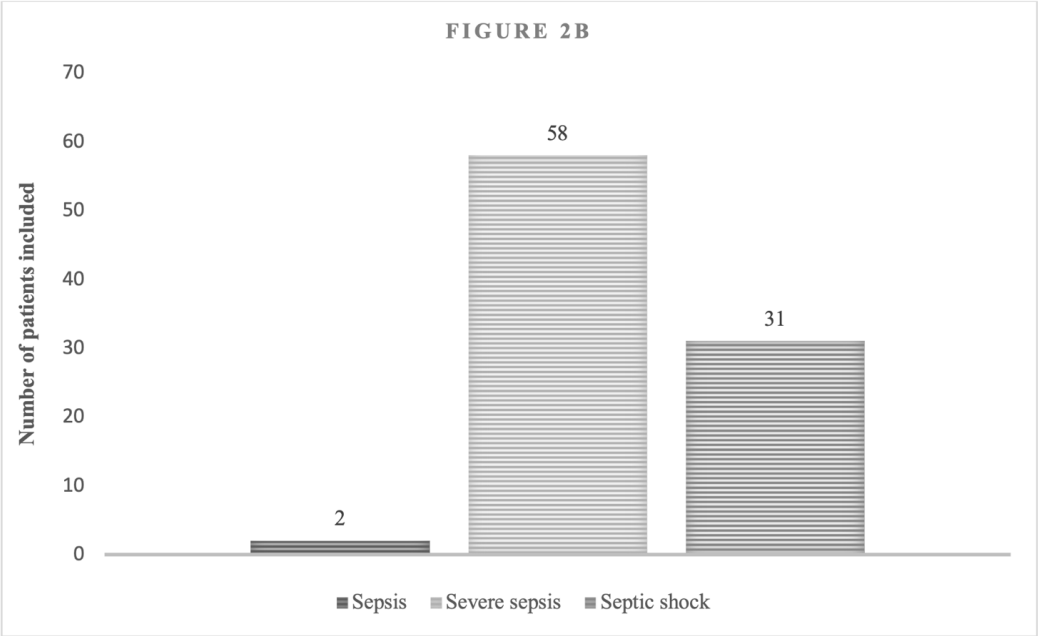


Figure 2. Patients' categorization as per IPSCC criteria [54] according to number of positive SIRS criteria (Fig. 2A) and to their definition of sepsis, severe sepsis and septic shock (Fig. 2B)

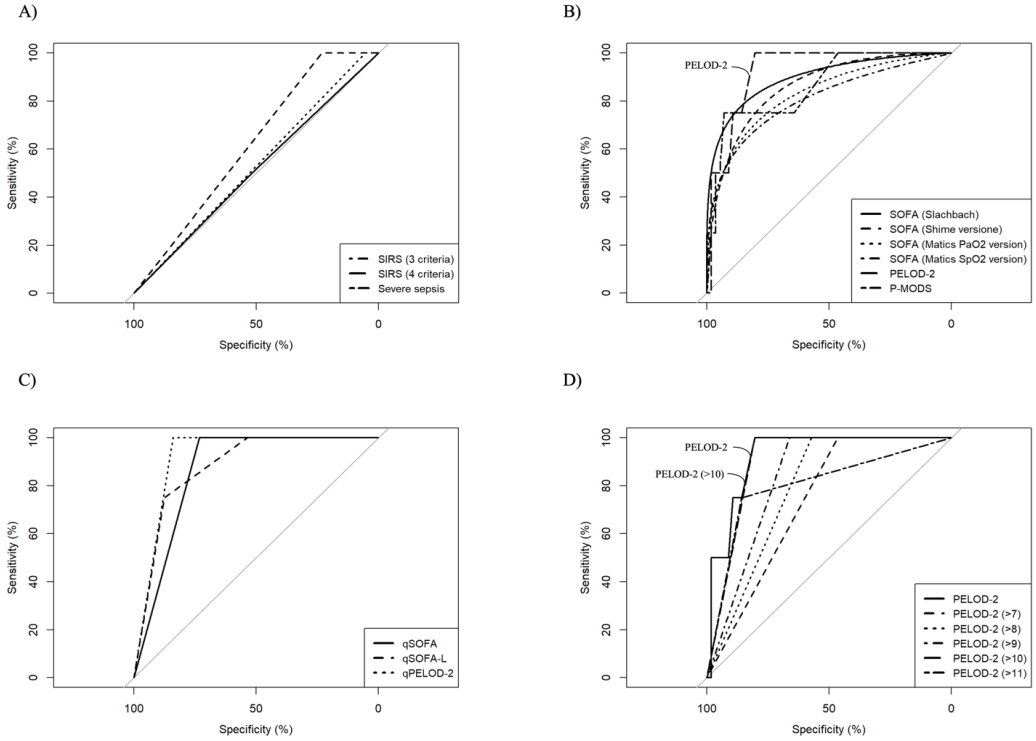


Figure 3. Comparison of AUROC curves at discriminating primary outcome (mortality). In particular: 3A) Comparison between SIRS 3 criteria, SIRS 4 criteria, severe sepsis; Fig. 3B) Comparison between SOFA (Schlapbach version), SOFA (Shime version), SOFA (Matics PaO2 version), SOFA (Matics SpO2 version), PELOD-2, P-MODS; Fig. 3C) Comparison between qSOFA, qSOFA-L, qPELOD-2; Fig 3D) Comparison between different cut-off levels for PELOD-2.

PHASE 3 & 4

WORKING PACKAGE 3

- **Creation of a national prospective database on pediatric patients with infection at the admission in the PICU.**
- **Timeline: June 2021 - February 2022**

We created a national study group and a national prospective database on critically ill pediatric patients admitted to the PICU with a diagnosis of infection. The database, which was named "SINN" ("Sepsis & Infection National Network"), is a part of the most comprehensive TIPNET database ("Network Collaborativo Permanente delle Terapie Intensive Pediatriche"). The TIPNET Italian Database is the only clinical quality registry of PICU patients in Italy. It is a prospective registry capturing patient demographics, severity, disease codes, and treatment interventions (registered on Milan's Ethics Committee). Eleven centers have joined the SINN database in the timeline.

The purpose of the study group and the national database was to create a database to inform the clinical, epidemiological, and prognostic characteristics of critically ill children admitted to the PICU with a diagnosis of infection in the Italian national territory. The creation of the database served as the platform for the conduction of a multi-center prospective study.

WORKING PACKAGE 4

- **Conduction of a multi-center prospective observational study on patients admitted to the PICU with a diagnosis of infection**
- **Timeline: February 2022 – December 2023**

We conducted a multi-center, prospective cohort study of critically ill children admitted to the PICU with a suspected infection at admission. We collected data related to the first 48 hours of admission of those patients ("Day-1" and "Day-2).

The aims were: a) to describe the characteristics of critically ill patients admitted to the PICU with a suspected infection; b) to compare the accuracy of several diagnostic criteria in defining sepsis, mainly comparing IPSCC criteria and organ-dysfunction based criteria; c) to compare the prognostic value of several organ dysfunction scores and other factors in predicting clinically relevant outcomes in patients with infection/sepsis.

Preliminary results of the study were presented as a Residency Thesis, confirming inadequate accuracy and prognostic performance of IPSCC scores and showing better results for organ-dysfunction scores in predicting mortality and morbidity.

SCIENTIFIC RESULTS

- **Results presented in November 2023 as a Residency Thesis in Pediatrics**
    - Candidate: Dr. Davide Padrin; Supervisor: Dr.ssa Angela Amigoni; Co-supervisors: Dr. Marco Daverio, Dr. Luca Marchetto
      "*Predictive value of prognostic and diagnostic scores performed in the first 48 hours in critically ill children admitted to PICU with infection:a multi-center cohort prospective study*"
- **The results were sent to the next ESPNIC Annual Meeting in Rome, 2024 in the form of the 3 abstracts (waiting for acceptance)**
    - **Marchetto L**, Comoretto RI, Zoppelletto F, Padrin D, Biban P, Ferrario S, Mondardini MC, Bordin G, Vitale P, Picconi E, Rulli I, Wolfler A, Gregori D, Amigoni A, Daverio M.
      Comparison of the Phoenix Sepsis Score with other prognostic scores in a cohort of children with infection admitted to the PICU: a multi-center Italian study
    - Padrin D, Comoretto RI, Scaravetti S, Di Michele L, Tessari A, Sacco F, Ferrario S, Eusebi G, Bordin G, Vitale P, Picconi E, Rulli I, Wolfler A, Gregori D, Daverio M, **Marchetto L.**
      Individual organ dysfunctions in children admitted to the PICU with infection: a multi-center Italian study
    - Daverio M, Comoretto RI, Alfisi A, Ceschia G, Padrin D, Tessari A, Sacco F, Ferrario S, Caramelli F, Bordin G, Conio A, Picconi E, Rulli I, Wolfler A, Gregori D, Enrico Vidal E, Amigoni, **Marchetto L.**
      AKI and RAI score association with clinically significant outcomes in childrenadmitted with infection to the PICU: a multicenter cohort study
- **The overall results will be sent for multiple peer-reviewed publications**

MANUSCRIPT (PHASE 3 & 4)

Currently still recruiting, we present preliminary results

BACKGROUND

Definition of pediatric sepsis

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.[58] Sepsis and septic shock have been a leading cause of morbidity and mortality for infants and children worldwide.[1-3] They are characterized by nonspecific physiologic abnormalities that encompass a heterogeneous population, and thus, they remain difficult to define, particularly in the pediatric population.[80] However, early identification and appropriate management in the initial hours after the development of sepsis improve outcomes,[50] and the development of tools capable of reliably and rapidly identifying sepsis may prove an invaluable aid to such improvements.

The cornerstones for the diagnosis of sepsis have always been the Systemic Inflammatory Response Syndrome (SIRS) criteria, which were described three decades ago as a clinical expression of the host response to inflammation. The clinical and biochemical hallmarks of such response were considered tachypnea, tachycardia, hyperthermia or hypothermia, leukocytosis or leukopenia.

Sepsis was termed as the development of SIRS in a patient with infection (see ***Figure 1***), potentially evolving to severe sepsis (i.e., sepsis complicated by organ dysfunction), and septic shock (i.e., sepsis with perfusion abnormalities), in order of increasing severity. This approach was codified by the consensus statement of the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) in 1992 and has been the predominant approach to classifying sepsis in the following years.[81] These definitions were developed for adult subjects and the 1992 consensus conference does not provide specific pediatric definitions.

The 1992 ACCP/SCCM Consensus Conference was followed by the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference (Sepsis-2), that maintained the definition of sepsis as the presence of both an infection and a systemic inflammatory response. However, initial diagnostic criteria for sepsis in the pediatric population were stated in this consensus conference, as the presence of signs and symptoms of inflammation plus infection with hyper- or hypothermia, tachycardia, and at least one

between altered mental status, hypoxemia, increased serum lactate level or bounding pulses.[82]

Specific criteria for pediatric sepsis were proposed in 2005 in the International Pediatric Sepsis Consensus Conference (IPSCC)[54] and have been widely adopted for use in clinical practice in the following years. Specifically, pediatric sepsis was defined as infection in the presence of at least two out of four SIRS criteria (***Figure e1, Appendix 2***); moreover, definitions for both severe sepsis and septic shock were also provided (***Table e1-e2, Appendix 2***).

In the last decade, the validity of SIRS criteria to identify and risk-stratify patients with sepsis has been challenged in adults, where insufficient sensitivity and specificity were demonstrated.[56,57]

On the verge of this considerations, in 2016, a Task Force convened by national societies including the SCCM and the European Society of Intensive Care Medicine (ESICM) proposed a new definition of sepsis, termed Sepsis-3.[58] This consensus emphasized that sepsis is differentiated from uncomplicated infection by the presence of life-threatening organ dysfunction as a result of a dysregulated host response to infection. The new definition abandoned the use of host SIRS criteria in identification of sepsis and eliminated the term severe sepsis.

The Sequential Organ Failure Assessment (SOFA) score, an organ-dysfunction score developed in 1994,[83] was selected as the scoring system to quantify organ dysfunction in the Sepsis-3. The Task Force validated the SOFA score in adult patients with suspected infection and found the SOFA system to be either comparable or superior to other scoring systems at discriminating in-hospital mortality. In particular, Singer et al.[56,59] analyzing 1.3 million electronic health record encounters, identified adults with suspected infection and observed that the predictive validity for in-hospital mortality of SOFA among Intensive Care Unit (ICU) encounters was statistically greater than SIRS, supporting its use as a diagnostic criteria of sepsis.

A simplified "quick" SOFA (qSOFA), including Glasgow Coma Scale (GCS), systolic blood pressure (SBP), and respiratory rate, had a good predictive validity for hospital mortality of patients outside the ICU.[59] The qSOFA score, incorporating only clinical parameters, has been suggested as manageable bedside tool to promptly identify infectious patients prone to poor outcomes, and could therefore be especially useful as a first screening tool for septic patients.

The Delphi process, systematic reviews, and development and validation cohorts leading to Sepsis-3 were based only adult populations and the Task Force recognized the need to develop similar updated definitions for pediatric populations.

Pediatric sepsis prognostic scores

Following the recent trends in the adult critical care research area, in the last two decades many authors explored the role of several disease scores to better identifying children with sepsis who are at a high risk of mortality to guide the escalation of therapy.

Previous works reported that SIRS criteria are met in > 90% of febrile children presenting to the PED, of which < 5% require Intensive Care Unit (ICU) admission,[55] since tachycardia and tachypnoea represent adaptive mechanisms commonly seen in almost every febrile childhood infection, including diseases with near-zero mortality (e.g., bronchiolitis).

On the other hand, Multiple Organ Dysfunction Syndrome (MODS) scores, which quantifies the presence of two or more organ dysfunctions, had been considered as a good alternative marker of severity of sepsis, mainly because MODS is the main cause of death and the final pathophysiological pathway of many diseases in the adult and pediatric ICU patient.[84]

It is with these considerations in mind, that modified pediatric SOFA scores[60-62] and the Pediatric-Multiple Organ Dysfunction (P-MODS) score for children were created.[68] A "quick", simplified version of pediatric SOFA has also been developed,[61] as well as a version considering lactates levels.[67] Another organ-dysfunction score, developed for pediatric patients admitted to the ICU, Pediatric Logistic Organ Dysfunction (PELOD) score-2,[64,65] has been tested in the pediatric population with variable results, as well as a simplified version.[65]

However, evidence about these scores is lacking in the pediatric population. Recent studies have tested the comparative performance of these scores in predicting poor outcome in pediatric sepsis, suggesting a central role for organ dysfunction scores to help standardize prognostication in pediatric sepsis.[85] Specifically, we conducted a mono-centric retrospective study[86] showing that IPSCC criteria have insufficient prognostic value for pediatric sepsis and that organ dysfunction scores seem to perform better in discriminating mortality and evaluating functional outcomes..

New sepsis definition

Until January 2024, pediatric sepsis definitions remained essentially based on the earlier sepsis definition (Sepsis-2)[54].

A task force was assembled in 2019 by the SCCM to update criteria for pediatric sepsis. A stepwise approach including a global surve, a systematic review and meta-analysis, a data- driven derivation and validation study was used to develop the new criteria, which culminated in the creation of the new Phoenix Criteria.[87,88] The Phoenix Score includes organ dysfuncion criteria of respiratory, cardiovascular, coagulation, and/or neurological systems.[87] The SCCM task force recommends that sepsis in children be identified by a Phoenix Sepsis Score of at least 2 points in children with suspected infection.

The Phoenix score was validated in a large cohort of patients in the first 24 hours of admission, demonstrating higher performance in predicting mortality compared to IPSCC criteria.

AIM OF THE STUDY

1. To describe the characteristics of critically ill patients admitted to Pediatric Intensive Care Units with a suspected infection.
2. To compare the accuracy of several diagnostic criteria in defining sepsis.
3. To compare the prognostic value of several organ dysfunction scores and other factors in predicting clinically relevant outcomes in patients with infection/sepsis
4. To compare the differet subcomponent of organ dyfunction scores in predicting clinically relevant outcomes in patients with infection/sepsis

METHODS

Study design

A multi-center prospective cohort study of critically ill children with a suspected infection at PICU admission is currently being performed. The study started in Febuary 2022 and is currently enrolling patients.

Participants

We are currently enrolling patients admitted to 12 PICUs participating to the Italian Network of Pediatric Intensive Care Units (TIPNet) registry. Inclusion criteria are: patients aged < 18 years old and patients with a “suspected infection” at PICU admission, defined as the initiation of a non-prophylactic antibiotic, antiviral, or antifungal therapy 24 hours prior the admission in the PICU or in the first 24 hours after admission (i.e., admission ± 24 hours), regardless of the main reason of their admission. Patients who required an escalation of a pre-existent prophylactic therapy for a suspected infection were also included. Each

PICU admission for the same patient was treated independently. Preterm neonates (< 37 weeks GA) were excluded from enrollment.

Data collection

Study data were collected and managed using REDCap electronic data capture tools hosted at Unit of Biostatistics, Epidemiology and Public Health – University of Padua.[89,90]

For every enrolled patient we collected several clinical and laboratory parameters in the first 48 hours of admission in the PICU. Specifically, data were collected in two different time intervals:

1. The first 24 hours of admission ("Day 1", from admission to the 24th hour post-admission)
2. The second 24 hours of admission ("Day 2", from the to the 25th to the 48th hour post-admission)

For every parameter we considered the "worst" value (see Vital signs and physiological parameters section below) documented in the considered time interval.

Vital signs and physiological parameters

Collected vital signs were weight, heart rate, systolic and diastolic blood pressure, respiratory rate, peripheral capillary oxygen saturation (SpO_2), temperature, level of consciousness (Glasgow Coma Scale, GCS), pupils.

Specifically:

1. Weight (g): we collected the highest value in the considered time-interval.
2. Heart rate (beats/min): we collected the highest and the lowest value in the considered time-interval.
3. Systolic and diastolic blood pressure (mmHg): we collected the lowest systolic value in the considered time-interval and the correspondent diastolic value of the same measured set.
4. Respiratory rate (beats/min): we collected the highest value in the considered time-interval.
5. SpO_2 (%): we collected the lowest value in the considered time-interval.
6. Temperature (°C): we reported whether the patient has a value outside the 36 – 38,5°C range in the considered time-interval.
7. GCS: we collected the worst score for every category of the scale in the considered time-interval; in an intubated patient we reported the worst GCS during the considered time-interval (e.g., 3/15 if completely sedated / unconscious, up to 11/15

in a spontaneously moving, open-eyes conscious patient; verbal component was considered as not assessable in this category of patients).

8. Pupils: we reported if the patient has anisocoria or fixed mydriasis in the considered time-interval.

Laboratory parameters and organ-dysfunction parameters

We collected parameters afferent to different organ-systems. If the parameter was not retrieved in the considered time-interval, it was considered normal.

Respiratory System

1. PaO_2 (mmHg): we collected the lowest value in the considered time-interval; if PaO_2 was absent the field was left empty;
2. $PaCO_2$ (mmHg): we collected the highest value in the considered time-interval; if $PaCO_2$ was absent because the patient did not get an arterial puncture or access, PvO_2 was recorded instead.
3. FiO_2 (%): we collected the highest value in the considered time-interval; FiO_2 was considered 21% for patients spontaneously breathing in room air and 30% for patients supported with low-flow oxygen-therapy systems (i.e., nasal cannula, simple oxygen mask).

Cardiovascular System

1. Lactates (mmol/L): we collected the highest value in the considered time-interval as well as the date and hour of the reported value in the considered time-interval; we also collected the date and hour of normalization of lactates, defined as the moment when lactates levels reduced at values ≤ 2 mmol/L if the patients previously had blood lactates levels > 2 mmol/L.
2. Vasopressors: we collected the maximum dose in the considered time-interval for all the following vasopressors: epinephrine (μg/kg/min), norepinephrine (μg/kg/min), dopamine (μg/kg/min), milrinone (μg/kg/min), dobutamine (μg/kg/min), vasopressin (UI/kg/min).

Renal system

1. Creatinine (μmol/L): we collected the highest value in the considered time-interval.
2. Urea (mmol/L): we collected the highest value in the considered time-interval.

Hematological System

1. White blood cells: we reported if the count is outside of the normal range for age (see ***Table e2, Appendix 2***).

2. Platelets (count * 10^6/mm^3): we collected the highest value in the considered time-interval.
3. Ferritin (μg/L): we collected the highest value in the considered time-interval.

Coagulation System

1. INR: we collected the highest value in the considered time-interval.
2. Fibrinogen (g/L): we collected the lowest value in the considered time-interval.
3. D-Dimer (μg/L): we collected the highest value in the considered time-interval.

Hepatic System

1. Bilirubin (μmol/L): we collected the highest value in the considered time-interval.
2. ALT (U/L): we collected the highest value in the considered time-interval.
3. Albumin (g/L): we collected the lowest value in the considered time-interval.

Other clinical parameters

We collected information about microbiology and antibiotic therapy, specifically:

1. Source of infection (if recognized).
2. Etiologic agent involved (if isolated)
3. Resistances of the etiologic agent involved (if isolated)
4. Type and class of the antimicrobial therapy initiated.

We reported whether patients needed extra-corporeal therapies during the admission (i.e., RRT, ECMO).

Sepsis Definition

Presence of sepsis and severe sepsis was defined based on the 2005 International Pediatric Sepsis Consensus Conference criteria (see ***Table e1-e2***). Since included patients had a suspected infection, those meeting SIRS criteria were defined as having sepsis. Criteria were applied to both Day 1 and Day 2 time-intervals.

Sepsis prognostic scoring

The following prognostic scores were calculated for all included patients for both Day 1 and Day 2 time-intervals:

Full scores

1. Pediatric Sequential Organ Failure Assessment Score (pSOFA) (see ***Table e3, Appendix 2***), in three different versions derived from literature.[60-62]
2. PEdiatric Logistic Organ Dysfunction 2 (PELOD-2) score (see ***Table e4, Appendix 2***)[64]

3. Pediatric Multiple Organ Dysfunction Score (P-MODS) (see ***Table e5, Appendix 2***).[68]
4. IPSCC severe sepsis criteria (see ***Table e3***)[54]

Quick scores

5. Pediatric Quick Sequential Organ Failure Assessment Score (qSOFA), with two different models based on the use of systolic or mean blood pressure (see ***Table e6, Appendix 2***).[61]
6. Pediatric Quick Sequential Organ Failure Assessment Score – Lactates (qSOFA-L), with two different models based on the use of systolic or mean blood pressure (see ***Table e7, Appendix 2***).[67]
7. Quick PEdiatric Logistic Organ Dysfunction 2 (qPELOD-2) score, with two different models based on the use of systolic or mean blood pressure (see ***Table e8, Appendix 2***).[65]

Organ dysfunction scores sub compontents

We calculated for each of the above described the different afferent sub-components of organ dysfunction, in particular dividing as following:

1. Neurologic component
2. Respiratory component
3. Cardiovascular component
4. Hepatic component
5. Hematological / Coagulative component
6. Renal component

Outcomes

The primary outcome of the study was mortality. Secondary outcomes were PICU length of stay (LOS), the duration of mechanical ventilation, the POPC score difference between PICU admission and discharge.

Sample size estimation

The primary outcome used to calculate the sample size was in-hospital mortality. The sample size estimation has been performed for a Poisson Monte Carlo experiment. The data have been generated 500 times drawing a random sample from a Poisson distribution with a rate parameter corresponding to 8 deaths over 100 patients admitted in PICU. For each simulated sample a Poisson 95% confidence interval (CI) has been computed. The average confidence interval length across Monte Carlo simulations has been computed. The experiment has been repeated over a sample size ranging from 100 to 300. The average Monte Carlo CI length according to the sample sizes has been reported in ***Figure 2***.

A sample size of 175 Septic patients will ensure a CI length for the mortality estimate of 0.09. Considering that 30% of the suspect sepsis patients are truly diagnosed as septic, the sample size should be increased to 584 (175/0.3) sepsis suspect patients to observe the outcome on 175 septic patients. The computations have been performed with the R 3.4.2 system.

Statistical analysis

The descriptive analysis of the sample is reported using the median and the interquartile range (IQR) (I-III quartile) for continuous variables and absolute numbers and relative percentages for categorical ones. Categorical variables were compared using the χ^2 test. Continuous variables were tested for normality and compared with the Mann-Whitney U test. The performance of each score to discriminate in- hospital mortality, mechanical ventilation duration, PICU length of stay and POPC difference was evaluated using the area under the receiver operating characteristics (AUROC) curve. Comparison between AUROC will be performed using the DeLong method. The statistical significance was set at a p value < 0.05. The analyses were performed using Stata 18 software.

Methodological and ethical considerations

The study was be conducted in compliance to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement on observational studies. The study was approved by the Ethics Committee as an amendment of the larger TIPNet registry.

Preliminary Results

Results shown below were obtained from **a preliminary analysis** based on data available at the moment of writing, while the study is still ongoing. Further analysis will be performed to analyze the single subcomponents of every organ dyscuntion score to understand the impact of different type organ dysfunction on clinical outcomes.

RESULTS

Patients' enrollment and characteristics

Enrollment started on March 2022 and is still ongoing at the moment of writing. 466 patients have been enrolled up until now from the 12 PICUs involved in the study.

Baseline characteristics of enrolled patients are summarized in ***Table 1*** below.

Overall, 261 patients (56.01%) met criteria for sepsis diagnosis according to the 2005 International Pediatric Sepsis Consensus Conference[54] in the first 24 hours after PICU admission. Patients meeting IPSCC sepsis criteria (Group 1 from here onwards) were of significantly older age (median 40.5 months versus 12.2 months) than patients non fulfilling IPSCC sepsis criteria (Group 2 from here onwards); no significant difference in both gender and ethnicity was noted.

Patients meeting sepsis criteria had a higher degree of comorbidities at admission (50.96% versus 38.05%), particularly in terms of oncologic/hematologic (13.79% versus 1.46%) and transplantology (3.45% versus 0%) comorbidities; this group of patients also showed a higher frequency of immunodeficiency (12.64% versus 1.46%).

Regarding organ dysfunction at admission, Group 1 patients showed a higher degree of cardiovascular (16.48% versus 3.90%), renal (11.88% versus 1.95%) and hematologic (12.64% versus 3.90%) dysfunction. The POPC score at admission showed no significant difference between the two groups, while there was a tendency towards lower POPC score at discharge in Group 1 patients. PIM-III score was significantly higher in Group 1 patients, with an expected mortality of 3.55% versus 1.54% for patients belonging to Group 2.

Infection and microbiology

Data about infection type and site, microbiology and antimicrobial therapy are summarized in ***Table e14*** (see ***Appendix 2***).

Overall, the most common infection site was the lower respiratory tract (55.36%), with a higher frequency in patients not meeting sepsis criteria diagnosis (63.41% versus 49.04% in patients meeting IPSCC sepsis criteria). Conversely, bloodstream infection was decisively more common in Group 1 patients relatively to Group 2 patients (7.66% versus 0.98%). Community-acquired infections were more frequent overall (86.48%), however patients belonging to Group 1 displayed a higher frequency of hospital-acquired infections (16.48% versus 9.76%) relatively to Group 2 patients.

Microbiological confirmation of infection (by either cultures, serology or molecular biology) was available in 60.43% of cases, with no significant difference between the two groups; conversely, in about 40% of cases microbiologic infection confirmation was not available and infection diagnosis was suspected based on clinical data alone. Viral infection was the most common overall (40.56%), followed by bacteria (26.18%), while mycotic and parasitic infection were globally uncommon. Sepsis patients had a significantly higher frequency of bacterial infection (34.87% versus 15.12%), while viral infection was more prevalent in non-sepsis patients (53.17% versus 30.65%). Among bacteria, *S. pneumoniae* was the most frequent microorganism overall (4.72%), while influenza virus was the most

common among viruses. Almost all fungal infection occurred in Group 1 patients and were mostly represented by *Candida* spp, with a single case of *Aspergillus* spp infection.

Almost all enrolled patients (93.78%) received antibiotic therapy, with an even higher frequency in patients meeting sepsis diagnosis criteria (98.08% versus 88.29%). The most frequently administered antibiotics were beta-lactams (88.20%), particularly penicillins (40.13%) and cephalosporins (41.85%), followed by macrolides (19.13%) and glycopeptides (18.67%). The use of carbapenems as well as linezolid at admission was significantly higher in patients belonging to Group 1 (12.81% versus 4.89% and 6.13% versus 2.44%, respectively).

Antiviral therapy was administered in 15.88% of cases overall, with no significant difference between the two groups. Conversely, antimycotic therapy was more frequently administered to patients meeting sepsis criteria (16.86% versus 7.32%), relatively to patients not meeting sepsis criteria.

Outcomes

Primary and secondary outcomes are reported in ***Table 2*** below. Global mortality was 4.63%. Death was significantly more frequent in patients meeting sepsis diagnosis criteria (6.61% versus 2.11%). Regarding secondary outcomes, Group 1 patients had a significantly longer PICU stay and mechanical ventilation duration, as well as a lower POPC at discharge.

Prognostic scores

Table 3 displays the distribution of all analyzed prognostic scores among enrolled patients at both Day 1 and Day 2 time-intervals. During the first 24 hours after admission all considered prognostic scores were higher among sepsis patients, relatively to non-sepsis patients.

Conversely, during Day-2 time-interval, organ dysfunction-based scores (pSOFA models) remained significantly different between Group 1 and Group 2 patients, whereas most vital signs-based scores (pediatric qSOFA and pediatric qSOFA-L models), as well as the P-MODS score, displayed no significant difference between the two groups. Conversely, qPELOD-2 models, other vital signs-based scores, maintained a significant difference between the two groups at the Day 2 time-interval.

Performance tests

Primary outcome

Predictive performance for the primary outcome (death) was tested for all analyzed prognostic scores measured at both time-intervals and compared to the predictive performance of the 2005 International Pediatric Sepsis Consensus Conference[54]criteria (see ***Figure*** *and* ***Figure***).

Globally, predictive performance for the primary outcome of the SIRS criteria were poor (AUROC 0,5210 - 0,638). All vital signs-based prognostic scores (pediatric qSOFA, pediatric qSOFA-L and qPELOD-2 models) had global poor performance as well, displaying no significant difference from SIRS criteria in primary outcome prediction, independently from considered time-interval.

Conversely, organ dysfunction-based scores, namely P-MODS and particularly pSOFA models, showed a significantly better prediction performance than SIRS criteria at both time-intervals. ***Table 5*** details performance test results for all prognostic scores group. The performance of the Day 1 and Day 2 measurements were tested against each other for every prognostic score, yielding no significant difference in predictive performance for the primary outcome (data not shown).

Secondary outcome – Mechanical ventilation

Neither sepsis diagnosis criteria nor any prognostic values showed any significant predictive capacity in regard to duration of mechanical ventilation, measured at the different cutoff of 3, 5 and 7 days. Results for a duration of mechanical ventilation of 5 days are detailed in ***Figure e4*** and ***Figure e5*** (see ***Appendix 2***).

Secondary outcome – PICU length of stay

Compared to sepsis diagnosis criteria, pSOFA scores measured at both Day 1 and Day 2 showed a significantly better, albeit still limited, prediction capacity in regard to PICU length of stay. qPELOD-2 and pqSOFA(-L) models showed to outperform sepsis criteria in predicting PICU length of stay only when measured at Day 2 time-interval. Performance tests were performed with different PICU length of stay cutoffs set at 3, 5, 7 and 10 days, with the 5-days cutoff yielding the most significant results. Results are detailed in ***Figure e6*** and ***Figure e7*** (see **Appendix 2**). Interestingly, the performance of most prognostic scores in predicting duration of PICU stay improved at the Day 2 time-interval in respect to the same scores measured at Day 1. These results are detailed in ***Figure e8*** (see ***Appendix 2***).

Secondary outcome – POPC score

Neither sepsis diagnosis criteria nor any prognostic values showed any significant predictive capacity in regard to POPC score difference between PICU admission and

discharge. Results for a duration of mechanical ventilation of 5 days are detailed in ***Figure e9*** and ***Figure e10*** (see ***Appendix 2***).

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DISCUSSION

In this multi-center prospective cohort study, we described baseline characteristics, microbiological and antimicrobial therapy data, outcomes measures in a sample of 466 children admitted to pediatric intensive care units adhering to the TIPNet network with a suspected or confirmed infection. We also evaluated the performance of various models of several pediatric prognostic scores (pediatric qSOFA, pediatric q-SOFA-L, pSOFA, qPELOD-2, and P-MODS) in predicting relevant outcomes in those patients, such as mortality, duration of mechanical ventilation, duration of PICU stay, functional status decline, and compared them to the current definition of pediatric sepsis, based on the 2005 International Pediatric Sepsis Consensus Conference (IPSCC).[54]

Our data show that patients admitted to PICU with infection and meeting sepsis diagnosis criteria according to IPSCC criteria are more frequently already burdened with morbidity than those not meeting sepsis criteria. Specifically, oncologic/hematologic and transplantologic patients admitted to the PICU may be diagnosed with sepsis more frequently; unsurprisingly, particularly fragile patients are more likely to develop severe and complicated infections, thus meeting SIRS criteria.

Regarding infection and microbiological data, it is interesting to note that lower respiratory tract infection was more prevalent in patients non diagnosed with sepsis, however the need for mechanical ventilation at admission showed no difference between the two groups of patients; this correlates with the higher frequency of viral rather than bacterial infection that we observed in non-sepsis patients, since these were most likely non-life threatening viral lower respiratory tract infection. Conversely, patients meeting sepsis criteria had a much higher frequency of bacterial and fungal infections; this is also unsurprising considering the higher tendency of these classes of microorganisms in evoking a systemic inflammatory response.

Considering our data on antimicrobial therapy, it is evident that patients meeting sepsis criteria were more likely to be administered antibiotic (and antimycotic) therapy and, among antibiotics, to be administered broad spectrum (e.g., carbapenems) or anti-MRSA (i.e., glycopeptides and linezolid) drugs. These results are to be correlated with the higher frequency of hospital-acquired infections displayed by the sepsis group: in-hospital developed infections occur in already morbid and fragile children, possibly with multi-drug resistant microbiological colonizations, thus causing more severe clinical phenotypes and prompting the use of broader spectrum antimicrobial therapy.

Patients meeting IPSCC diagnostic criteria for sepsis had a worse trend across all clinically relevant outcomes: this group had a higher mortality rate, longer mechanical

ventilation and PICU stay durations, and a tendency towards a larger decline in functional status as described by the variation in POPC score. In this regard, current pediatric sepsis diagnosis criteria seem to be adequately describing severity in infection in children. However, as we already discussed, their prognostic capacity has already been questioned in the last two decades in the adult population,[56] resulting in a paradigmatic change during last Sepsis-3 Consensus Statement.[58] In particular, as mentioned before, the consensus resulted in the elimination of the definitions of SIRS and severe sepsis, underlining that sepsis is already differentiated from uncomplicated infection by the presence of life-threatening organ dysfunction as a result of a dysregulated host response to infection. The operationalization of clinical criteria to identify individuals meeting outcomes consistent with sepsis in Sepsis-3 has conducted to the implementation of SOFA score, which is now considered the gold standard to grade organ dysfunction in adult patients with suspected infection.

Several prognostic scores have been developed in order to enhance prognostication, patient classification, research and quality monitoring. Recent studies have made an effort to validate these prognostic scores on large pediatric populations. Our study is the first multi-centric prospective pediatric study with a large sample size aiming to establish the ability of these tools to reliably identify patients with poor prognosis in the first hours following PICU admission.

We found that the IPSSC criteria were very poor predictor of both mortality and the other clinically relevant outcomes we measured (mechanical ventilation duration, PICU length of stay, functional status decline). Conversely, organ dysfunction-based scores, such as the pSOFA models and particularly the Shime version[18], performed the best among the analyzed prognostic scores, particularly in regard to mortality and, to a lesser extent, PICU length of stay; performance in prognostication of mechanical ventilation duration and POPC score difference were instead unsatisfactory and not significantly better than that of the IPSSC criteria. The “quick”, vital signs-based scores (pqSOFA, pqSOFA-L, qPELOD-2 models) displayed an unimpressive predictive performance across all analyzed outcomes, barely managing to outperform the IPSCC criteria. Lastly, the P-MODS score yielded mixed results, with prognostic performance showing mostly unsatisfactory results, albeit still better than those of the vital signs-based scores.

Interestingly, regarding the PICU length of stay secondary outcome, prognostic score measured at the 25-48 hour after PICU admission time-interval (Day 2 in our study) appear to have a better performance than the same scores measured in the first 24 hours following admission. This may reflect the fact that patients who display a better response to resuscitation maneuvers, and quickly ameliorate their organ dysfunctions in the first hours after PICU admission, are more likely to have a quicker discharge from PICU. However, this

effect does not appear to translate in a reduction in mortality, as the predictive performance for mortality any of the analyzed scores was similar independently of the score being measured at Day 1 or Day 2.

These results suggest that the presence of organ dysfunction, highlighted by the pSOFA models, is the main element that is really predictive of poor prognosis, whereas the presence of vital signs alterations is mostly insufficient in discriminating patient that will have a worse outcome. IPSCC criteria should instead be abandoned as they lack diagnostic accuracy in predicting mortality and other bad outcomes. Although the last guidelines on pediatric sepsis published by the Surviving Sepsis Campaign[7] still relied on the 2005 pediatric sepsis definitions, they acknowledged the need to update the actual definitions for pediatric population.

Lastly, even the best performing prognostic scores (i.e., pSOFA models), while having very good performance in predicting mortality, are still lacking in regard to predicting the morbidity burden of sepsis survivors.

CONCLUSIONS

We described the clinical and microbiological characteristics as well as outcome measures and a large array of prognostic scores in a large cohort of pediatric patients admitted to PICU with infection. International Pediatric Sepsis Consensus Conference criteria had poor prognostic value across all measured outcomes. Organ dysfunction-based scores, specifically pSOFA models, showed the best performance in predicting mortality and PICU length of stay in this cohort of patients, however prediction performance for mechanical ventilation duration and decline in functional status is lacking. “Quick” vital signs-based prognostic scores lack prognostic capacity and are insufficient in discriminating patients with poor outcome.

Further analysis at the end of recruitment will include the comparison between the new Phoenix score and other organ-dysfunction criteria.

Characteristics	Overall	Group 1 (SIRS criteria met at 24h)	Group 2 (SIRS criteria not met at 24h)	*p* value
	N = 466 (100%)	**N = 261 (56.01%)**	**N = 205 (43.99%)**	
Age, months (IQR)	27.0 (4.5 – 77.0)	40,5 (13,7 - 111,8)	12,2 (2,3 - 40,6)	< 0.001
Gender				
Female, no (%)	198 (42.49%)	115 (44.06%)	83 (40,49%)	0.735
Male, no (%)	266 (57.08%)	145 (55.56%)	121 (59,02%)	
Ambiguous, no (%)	2 (0.43%)	1 (0.38%)	1 (0,49%)	
Weight, kg (IQR)	12 (6 - 20)	15 (9 - 28)	8,8 (4,8 - 15)	< 0.001
Ethnicity				
African, no (%)	23 (4.94%)	14 (5.36%)	9 (4,39%)	
Arabian, no (%)	49 (10.52%)	27 (10.34%)	22 (10,73%)	
Asiatic, no (%)	29 (6.22%)	17 (6.51%)	12 (5,85%)	0,982
Caucasian, no (%)	344 (73.82%)	190 (72.80%)	154 (75,12%)	
Hispanic, no (%)	10 (2.15%)	6 (2.30%)	4 (1,95%)	
Mixed, no (%)	11 (2.36%)	7 (2.68%)	4 (1,95%)	
Comorbidities				
Any, no (%)	211 (45.28%)	133 (50,96%)	78 (38,05%)	0,005
Respiratory, no (%)	37 (7.94%)	20 (7,66%)	17 (8,29%)	0,803
Cardiologic, no (%)	33 (7.08%)	19 (7,28%)	14 (6,83%)	0,851
Metabolic, no (%)	11 (2.36%)	6 (2,30%)	5 (2,44%)	0,921
Neurologic, no (%)	73 (15.67%)	44 (16,86%)	29 (14,15%)	0,424
Neuromuscular, no (%)	18 (3.86%)	11 (4,21%)	7 (3,41%)	0,656
Oncologic/hematologic, no (%)	39 (8.37%)	36 (13,79%)	3 (1,46%)	< 0,001
Renal, no (%)	11 (2.36%)	8 (3,07%)	3 (1,46%)	0,258
Gastroenterological, no (%)	21 (4.51%)	12 (4,60%)	9 (4,39%)	0,915
Prematurity, no (%)	29 (6.22%)	12 (4,60%)	17 (8,29%)	0,101
Syndromic, no (%)	46 (8.29%)	29 (11,11%)	17 (8,29%)	0,311
Malformative, no (%)	32 (6.87%)	21 (8,05%)	11 (5,37%)	0,256
Transplantology, no (%)	9 (1.93%)	9 (3,45%)	0 (0%)	0,007
Other, no (%)	16 (3.43%)	14 (5,36%)	2 (0,98%)	0,01
Organ dysfunction				
Any, no (%)	412 (88.41%)	226 (86,59%)	186 (90,73%)	0,166
Respiratory, no (%)	361 (77.47%)	197 (75,48%)	164 (80,00%)	0,246
Cardiovascular, no (%)	51 (10.94%)	43 (16,48%)	8 (3,90%)	< 0,001
Neurologic, no (%)	66 (14.16%)	39 (14,94%)	27 (13,17%)	0,586
Renal, no (%)	35 (7.51%)	31 (11,88%)	4 (1,95%)	< 0,001
Hematologic, no (%)	41 (8.80%)	33 (12,64%)	8 (3,90%)	0,001
Hepatic, no (%)	19 (4.08%)	12 (460%)	7 (3,41%)	0,522
Immunodeficiency, no (%)	36 (7.73%)	33 (12,64%)	3 (1,46%)	< 0,001

POPC score admission				
1	273 (60.00%)	143 (55,64%)	130 (65,66%)	0,31
2	67 (14.73%)	41 (15,95%)	26 (13,13%)	0,355
3	47 (10.33%)	30 (11,67%)	17 (8,59%)	0,255
4	65 (14.29%)	41 (15,95%)	24 (12,12%)	0,216
5	3 (0.66%)	2 (0,78%)	1 (0,51%)	0,709
POPC score discharge				
1	219 (53.28%)	108 (47,79%)	111 (60,00%)	0,046
2	86 (20.92%)	50 (22,12%)	36 (19,46%)	0,659
3	46 (11.19%)	33 (14,60%)	13 (7,03%)	0,024
4	55 (13.38%)	31 (13,72%)	24 (12,97%)	0,955
5	5 (1.22%)	4 (1,77%)	1 (0,54%)	0,277
PIM-III score, % (IQR)	2,47 (0.65 – 5.48)	3,55 (0,95 - 6,62)	1,54 (0,55 - 4,28)	< 0,001

Table 1. Baseline characteristics of enrolled patients.

Characteristics	**Overall**	**Group 1 (SIRS criteria met at 24h)**	**Group 2 (SIRS criteria not met at 24h)**	***p* value**
Primary outcome				
Death, no (%)	20 (4,63%)	16 (6,61%)	4 (2,11%)	0,027
Secondary outcomes				
PICU LOS, days (IQR)	5 (2 - 10)	5,5 (3 - 11)	4 (2 - 8)	0,0016
MV duration, days (IQR)	3 (1 - 8)	4 (2 - 9)	3 (1 - 6)	0,0026
POPC difference, n (IQR)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0,0359

Table 2. Primary and secondary outcomes summary.

Characteristics	Overall	Group 1 (SIRS criteria met at 24h)	Group 2 (SIRS criteria not met at 24h)	*p* value
Prognostic scores Day 1				
pSOFA (Schlapbach), n (IQR)	6 (4 - 9)	7 (4 - 10)	6 (4 - 7)	0,0121
pSOFA (Matics, paO2), n (IQR)	9 (7 - 13)	10 (7 - 14)	8 (7 - 10)	0,0048
pSOFA (Shime), n (IQR)	6 (4 - 9)	6 (4 - 11)	5 (3 - 7)	0,0036
Pediatric qSOFA (MAP), n (IQR)	2 (2 - 3)	2 (2 - 3)	2 (1 - 3)	< 0,0001
Pediatric qSOFA (SBP), n (IQR)	2 (1 - 2)	2 (2 - 2)	2 (1 - 2)	0,0002
Pediatric qSOFA-L (MAP), n (IQR)	3 (2 - 3)	3 (3 - 2)	2 (2 - 3)	< 0,0001
Pediatric qSOFA-L (SBP), n (IQR)	2 (2 - 3)	2 (2 - 3)	2 (1 - 3)	0,0003
qPELOD-2 (MAP), n (IQR)	1 (0 - 2)	1 (0 - 2)	1 (0 - 1)	0,0001
qPELOD-2 (SBP), n (IQR)	1 (0 - 1)	1 (0 - 2)	1 (0 - 1)	0,0015
P-MODS, n (IQR)	4 (2 - 7)	5 (3 - 7)	3 (2 - 5)	0,0015
Prognostic scores Day 2				
pSOFA (Schlapbach), n (IQR)	6 (4 - 9)	7 (4 - 10)	5 (3 - 6,5)	0,0062
pSOFA (Matics, paO2), n (IQR)	9,5 (6 - 13)	10 (7 - 13)	8,5 (6 - 10)	0,0096
pSOFA (Shime), n (IQR)	6 (3 - 9)	7 (3 - 10)	4,5 (3 - 6)	0,0048
Pediatric qSOFA (MAP), n (IQR)	2 (1 - 2)	2 (1 - 2)	2 (1 - 2)	0,2579
Pediatric qSOFA (SBP), n (IQR)	2 (1 - 2)	2 (1 - 2)	1 (1 - 2)	0,7676
Pediatric qSOFA-L (MAP), n (IQR)	2 (1 - 3)	2 (1 - 3)	2 (1 - 3)	0,6139
Pediatric qSOFA-L (SBP), n (IQR)	2 (1 - 2)	2 (1 - 2)	2 (1 - 2)	0,1951
qPELOD-2 (MAP), n (IQR)	1 (0 - 1)	1 (0 - 1)	0 (0 - 1)	0,012
qPELOD-2 (SBP), n (IQR)	0 (0 - 1)	1 (0 - 1)	0 (0 - 1)	0,0105
P-MODS, n (IQR)	3,5 (1 - 6)	4 (1,5 - 6)	2 (1 - 5)	0,0643

Table 4. Prognostic scores distribution in enrolled patients

Score	AUROC	Standard error	χ^2 value	*p* value
Day 1				
pSOFA models				
Sepsis criteria	0.5774	0.0510		
pSOFA (Schlapbach)	0.8789	0.0384	61.2470	0.0000
pSOFA (Matics, paO2)	0.8855	0.0339	49.5064	0.0000
pSOFA (Shime)	0.9211	0.0233	61.3798	0.0000
pqSOFA models				
Sepsis criteria	0.6328	0.0468		
pqSOFA (SBP)	0.6847	0.0606	0.4724	0.4919
pqSOFA (MAP)	0.6355	0.0613	0.0014	0.9701
pqSOFA-L (SBP)	0.7354	0.0615	1.5487	0.2133
pqSOFA-L (MAP)	0.7065	0.0634	0.8214	0.3648
qPELOD-2 models				
Sepsis criteria	0.6398	0.0467		
qPELOD-2 (SBP)	0.6778	0.0757	0.1875	0.6650
qPELOD-2 (MAP)	0.6609	0.0701	0.0766	0.7820
P-MODS				
Sepsis criteria	0.5979	0.0422		
P-MODS	0.8168	0.0752	13.1925	0.0003
Day 2				
pSOFA models				
Sepsis criteria	0.2510	0.0595		
pSOFA (Schlapbach)	0.8857	0.0381	66.5125	0.0000
pSOFA (Matics, paO2)	0.8627	0.0412	42.9928	0.0000
pSOFA (Shime)	0.8835	0.0398	51.3914	0.0000
pqSOFA models				
Sepsis criteria	0.6156	0.0494		
pqSOFA (SBP)	0.5739	0.0659	0.3649	0.5458
pqSOFA (MAP)	0.6322	0.0649	0.0477	0.8271
pqSOFA-L (SBP)	0.6494	0.0701	0.2093	0.6474
pqSOFA-L (MAP)	0.6864	0.0694	0.7899	0.3741
qPELOD-2 models				
Sepsis criteria	0.6170	0.0493		
qPELOD-2 (SBP)	0.7609	0.0546	3.7342	0.0533
qPELOD-2 (MAP)	0.7919	0.0366	9.8113	0.0017
P-MODS				
Sepsis criteria	0.5258	0.0596		
P-MODS	0.7739	0.0783	11.0764	0.0009

Table 5. Details of predictive performance for death for all prognostic scores measured at both Day 1 and Day 2 time-intervals, compared to SIRS criteria.

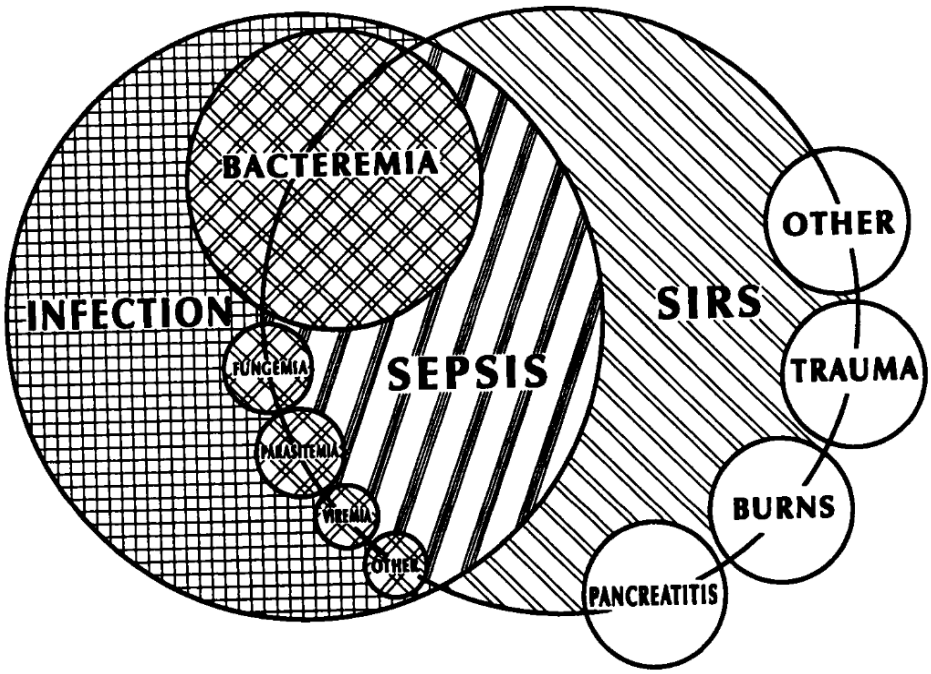

Figure 1. Relationship between infection, systemic inflammatory response syndrome and sepsis according to the 1992 ACCP/SCCM consensus conference.[82]

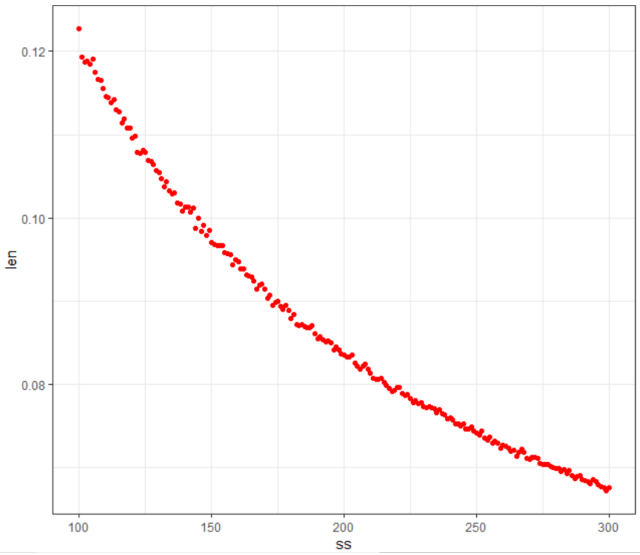

Figure 2. Average Monte Carlo CI length according to the sample size.

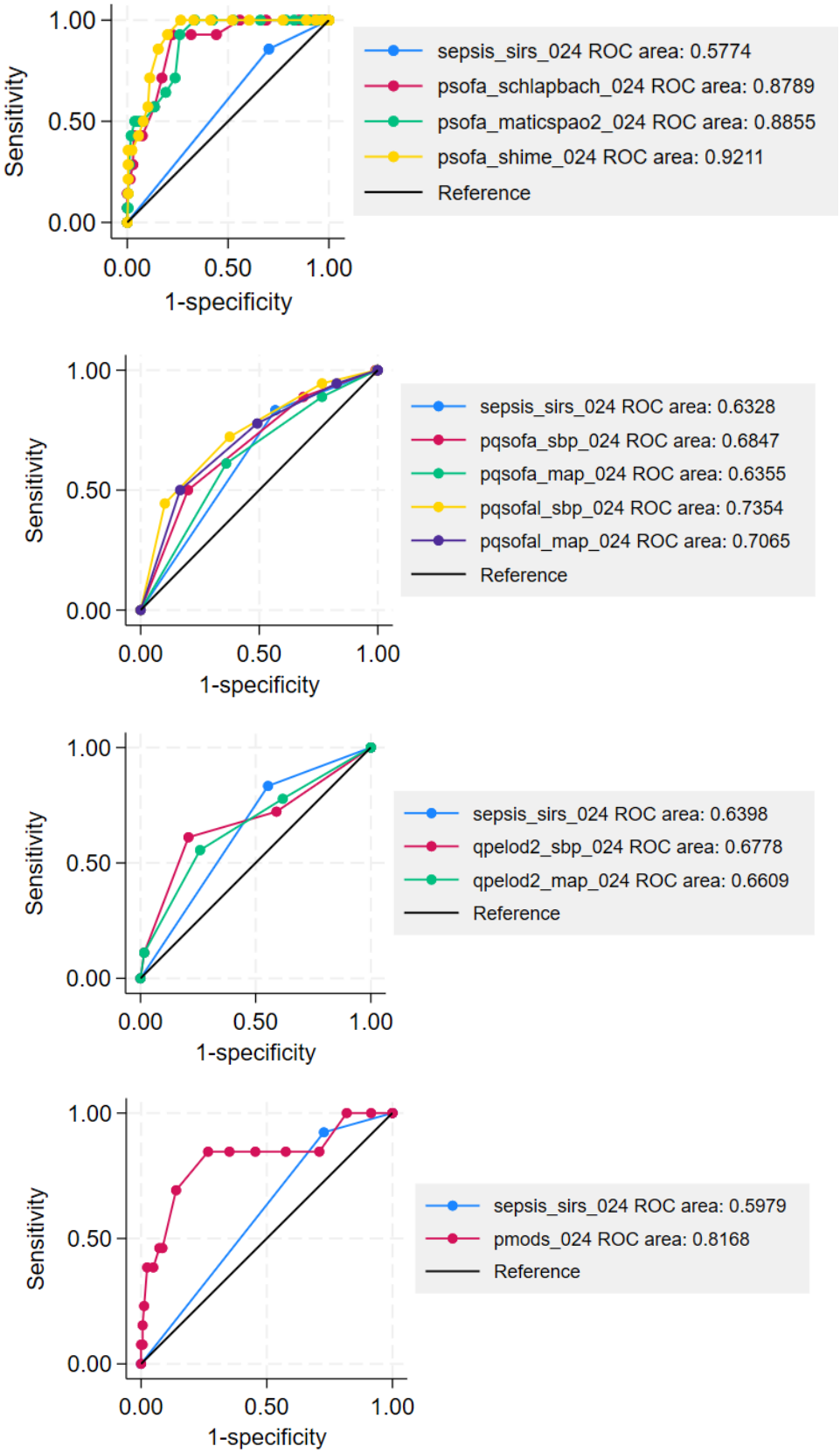

Figure 3. Predictive performance for mortality for all prognostic scores measured at the Day 1 time-interval, compared to SIRS criteria.

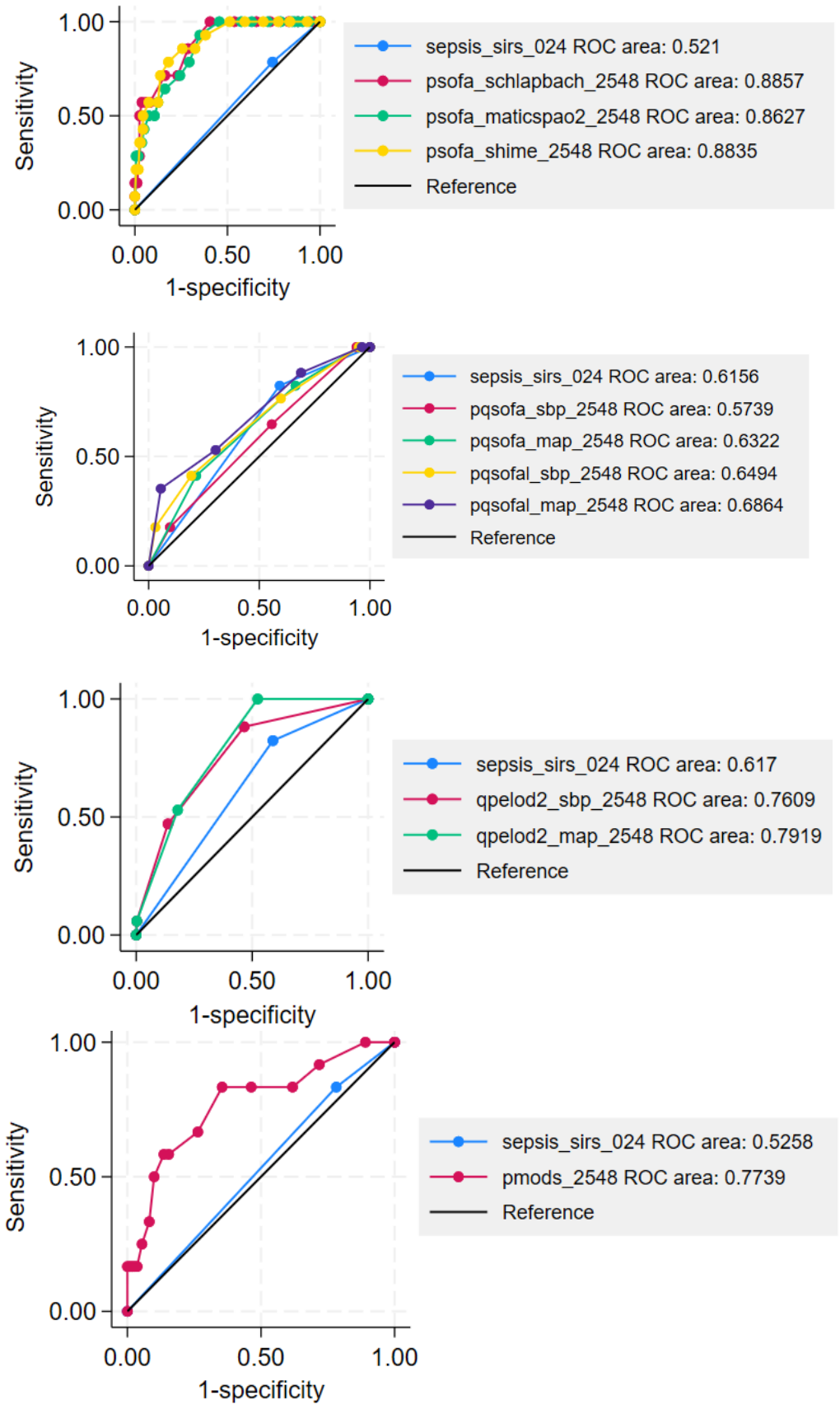

Figure 4. Predictive performance for mortality for all prognostic scores measured at the Day 2 time-interval, compared to SIRS criteria.

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APPENDIX

Appendix 1 (Supplementary Content)

Systematic Review

Appendix 2 (Supplementary Content)

Single-Center Retrospective Observational Cohort Study and Multi-Center Prospective Observational Cohort Study

Appendix 1. Supplemental Digital Content

Outcomes of pediatric fluid-refractory septic shock according to different vasoactive strategies: A systematic review and meta-analysis

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Summary of Content

Supplemental Methods

Table S1. Research question according to PICO

Population	Pediatric patients under 18 years of age with fluid-refractory septic shock (FRSS)
Intervention	Initial vasoactive treatment with 1 or 2 agents
Comparison	*Nil a priori* Another vasoactive agent if available
Outcomes	i. *Primary:* All-cause mortality ii. *Secondary:* proportion of patients with shock resolution at a defined time, time to shock resolution, duration of vasoactive support (or vasoactive-free days), need for mechanical ventilation (MV), duration of MV (or ventilation-free days), PICU and hospital length of stay (LOS), organ dysfunction scores at a defined time (or organ-failure free days)

Table S2. Search Strategies

The selected terms for the analysis are divided in three groups: **Group 1** contains terms regarding the pediatric age combined with the Boolean operator OR, **Group 2** contains terms regarding septic shock with the Boolean operator OR, Group 3 contains terms regarding the administration of vasoactive. These three groups will be combined with the Boolean operator AND for the search.

The subsequent databases and queries were used for the search:

- **MEDLINE/PubMed**

#1	(“Child”[Mesh] OR “Child, preschool”[Mesh] OR “Infant”[Mesh] OR child* OR children OR paediatr* OR pediatr* OR adolescen* OR youth* OR teen* OR infant* OR infancy OR toddler* OR kid OR kids OR baby OR babies OR neonat*)
#2	(“Sepsis”[Mesh] OR "Shock, Septic"[Mesh] OR “Shock”[Mesh] OR “septic shock” OR shock OR sepsis OR “refractory shock” OR bacterial infection*)
#3	("vasoconstrictor agents"[Mesh] OR inotrope OR inotropes OR vasopressor OR vasopressors OR vasoactive OR vasoactive drug* OR vasoactive agent* OR dopamine OR epinephrine OR adrenaline OR norepinephrine OR noradrenaline OR dobutamine OR milrinone OR vasopressin OR terlipressin)
#4	#1 AND #2 AND #3

- **CINAHL/EBSCO**

#1	child* OR children OR paediatr* OR pediatr* OR infant* OR infancy OR adolescen* OR youth* OR teen* OR toddler* OR kid* OR baby OR babies OR neonate OR neonates OR adolescent
#2	“septic shock” OR shock OR sepsis OR “refractory shock” OR “bacterial infection”

#3	inotrope OR inotropes OR vasopressor OR vasopressors OR vasoactive OR "vasoactive drug" OR "vasoactive agent" OR dopamine OR epinephrine OR adrenaline OR norepinephrine OR noradrenaline OR dobutamine OR milrinone OR vasopressin OR terlipressin
#4	#1 AND #2 AND #3

- **The Cochrane Library**

#1	child* OR children OR paediatr* OR pediatr* OR infant* OR infancy OR adolescen* OR youth* OR teen* OR toddler* OR kid* OR baby OR babies OR neonate OR neonates OR adolescent
#2	MeSH descriptor: [Child] explode all trees
#3	#1 OR #2
#4	"septic shock" OR shock OR sepsis OR "refractory shock" OR "bacterial infection"
#5	MeSH descriptor: [Shock, Septic] explode all trees
#6	#4 OR #5
#7	inotrope OR inotropes OR vasopressor OR vasopressors OR vasoactive OR "vasoactive drug" OR "vasoactive agent" OR dopamine OR epinephrine OR adrenaline OR norepinephrine OR noradrenaline OR dobutamine OR milrinone OR vasopressin OR terlipressin
#8	MeSH descriptor: [Vasoconstrictor Agents] explode all trees
#9	#7 OR #8
#10	#3 AND #6 AND #9

- **SCOPUS**

#1 TITLE-ABS-KEY(child* OR children OR paediatr* OR pediatr* OR adolescen* OR youth* OR teen* OR infant* OR infancy OR toddler* OR kid OR kids OR baby OR babies OR neonat*)

#2 TITLE-ABS-KEY("septic shock" OR shock OR sepsis OR "refractory shock" OR "bacterial infection")

#3 TITLE-ABS-KEY(inotrope OR inotropes OR vasopressor OR vasopressors OR vasoactive OR "vasoactive drug" OR "vasoactive agent" OR dopamine OR epinephrine OR adrenaline OR norepinephrine OR noradrenaline OR dobutamine OR milrinone OR vasopressin OR terlipressin)

#4 #1 AND #2 AND #3

- **Web of Science**

#1 TS=(child* OR children OR paediatr* OR pediatr* OR adolescen* OR youth* OR teen* OR infant* OR infancy OR toddler* OR kid OR kids OR baby OR babies OR neonat*)

#2 TS=("septic shock" OR shock OR sepsis OR "refractory shock" OR "bacterial infection")

#3 TS=(inotrope OR inotropes OR vasopressor OR vasopressors OR vasoactive OR "vasoactive drug" OR "vasoactive agent" OR dopamine OR epinephrine OR adrenaline OR norepinephrine OR noradrenaline OR dobutamine OR milrinone OR vasopressin OR terlipressin)

#4 #1 AND #2 AND #3

- **Embase**

#1	child* OR children OR paediatr* OR pediatr* OR infant* OR infancy OR adolescen* OR youth* OR teen* OR toddler* OR kid* OR baby OR babies OR neonate OR neonates OR adolescent OR 'children'/exp
#2	'septic shock' OR shock OR sepsis OR 'refractory shock' OR 'bacterial infection' OR 'septic shock'/exp
#3	inotrope OR inotropes OR vasopressor OR vasopressors OR vasoactive OR vasoactive drug OR vasoactive agent OR dopamine OR epinephrine OR adrenaline OR norepinephrine OR noradrenaline OR dobutamine OR milrinone OR vasopressin OR terlipressin OR 'vasoactive agent'/exp
#4	#1 AND #2 AND #3

- **ClinicalTrials.GOV**

(children OR pediatr* OR paediatr*) AND (septic shock OR sepsis) AND (vasoactive OR vasopressor* OR inotrope OR vasoactive agent)

- **metaRegister of Controlled Trials**

(child* OR children OR pediatr* OR paediatr* OR infant*) AND (septic shock or sepsis OR "refractory shock") AND (vasoactive OR vasopressor* OR inotrope OR vasoactive agent OR epinephrine OR adrenaline OR norepinephrine OR noradrenaline OR dopamine)

Tables

Table S3. Studies reporting outcomes on patient undergoing 1 vasoactive agent for FRSS

First Author, Year	Study Design	Single vs Multi-center, Study Period, Country	Inclusion Criteria	Definitions of Sepsis, Septic Shock & FRSS ("trigger to vasoactive")	Trigger-To-Vasoactive	N. of Patients on 1 Vasoactive Agent	Vasoactive Received (Drug, Dosage, Duration)	Reason for change / escalation to more vasoactives	Age (cohort)	Adjunctive Therapies	Mortality Rate (Primary Outcome)	Secondary Outcomes
Ventura, 2015[1]	RCT	Single-center, 2009 – 2013, Brazil (UMIC)	1 mo – 15 yrs with FRSS	• **Severe sepsis:** ACCM/PALS guidelines definition • **FRSS:** persistence of signs of hypoperfusion after 40 ml/kg crystalloids	After randomization – 3.2 ± 3.1 h mean ± SD	63 pts	**Dopamine** (range 5 – 10 mcg/kg/min) until shock resolution or maximum dose, followed by drug of clinicians' choice	After 60 minutes and three further increases of selected drug with no clinical response	39.6 mo ± 46.3, mean ± SD	*Other vasoactive:* 33 pts (52.4%) *Hydrocortisone:* 21 pts (33.3%) *MV:* 62 pts (98.4%) *RRT:* 11 pts (17.5%)	*28-day mortality* 13 pts (20.6%)	*Duration of resuscitation:* 33.6 hour ± 57, mean ± SD *Vasoactive drug-free days*: 18.9 days ± 11.3, mean ± SD *MV-free days: 16.3* days ± 10.6, mean ± SD
					After randomization – 2.4 ± 1.9 h mean ± SD	57 pts	**Epinephrine** (range 0.1 – 0.3 mcg/kg/min) until shock resolution or maximum dose, followed by drug of clinicians' choice	After 60 minutes and three further increases of selected drug with no clinical response	56.9 mo ± 58.2, mean ± SD	*Other vasoactive:* 22% (38.6%) *Hydrocortisone:* 17 pts (29.8%) *MV:* 51 pts (89.5%) *RRT:* 6 pts (10.5%)	*28-day mortality* 4 pts (7.0%)	*Duration of resuscitation:* 16.1 hour ± 23.6, mean ± SD *Vasoactive drug-free days:* 23.7 days ± 9, mean ± SD *MV-free days: 18.6* days ± 10.3, mean ± SD
Fernandez, 2016[2]	Retrospective Cohort Study	Single-center, 2008 – 2013, Colombia (UMIC)	1 mo – 18 yrs with crystalloid-refractory septic shock	• Not reported	Not reported	70 pts	**Norepinephrine** (range 0.01 – 1 mcg/kg/min) Until maximum dose of 1 mcg/kg/min, followed by vasopressin	Not responding to 1 mcg/kg/min of norepinephrine, followed by vasopressin	50 mo ± 60, mean ± SD	/	*28-day mortality:* 12 pts (17.1%)	/
Ramaswamy, 2016[3]	RCT	Single-center, 2013 – 2014, India (LMIC)	3 mo – 12 yrs with fluid-refractory hypotensive cold septic shock	• **Septic shock:** sepsis including cardiovascular dysfunction (hypotension according to PALS vitals or 2 signs of poor perfusion) • **FRSS:** hypotension and poor perfusion after 40 ml/kg crystalloids	After randomization – not reported timing	31 pts	**Dopamine** (range 10 – 20 mcg/kg/min) Until shock resolution or maximum dose, followed by open-label epinephrine	After 30 minutes and three further increases of selected drug with no clinical response	4 (0.8 – 8) yrs, median (IQR)	*Steroids*: 24 pts (77.4%) *MV*: 28 pts (90.3%)	*28-day mortality:* 18 pts (58.1%)	*Resolution of shock:* 4 pts (12.9%) *Organ failure-free days:* 20 (18.5-24) days, median (IQR) *Duration MV:* 7.0 (3.0-11.5) days, median (IQR) *SOFA day 3:* 12 (6-14), median (IQR) *ICU LOS:* 7 (5-12) days, median (IQR) *Hospital LOS:* 11 (9-13) days, median (IQR)
					After randomization – not reported timing	29 pts	**Epinephrine** (range 0.1 – 0.3 mcg/kg/min) Until shock resolution or maximum dose, followed by open-label epinephrine	After 30 minutes and three further increases of selected drug with no clinical response	7 (1 – 11) yrs, median (IQR)	*Steroids:* 20 pts (69.0%) *MV:* 19 (65.5%)	*28-day mortality:* 14 pts (48.3%)	*Resolution of shock:* 12 pts (41.4%) *Organ failure-free days:* 24 (23-26) days, median (IQR) *Duration MV:* 7.9 (3.7-7.9) days, median (IQR) *SOFA day 3:* 8 (2-13), median (IQR) *ICU LOS:* 8 (4-12) days, median (IQR) *Hospital LOS:* 9 (8-17) days, median (IQR)
Ranjit, 2016[4]	Retrospective Cohort Study	Single-center, 2014 – 2015, India (LMIC)	1 mo – 16 yrs with fluid-refractory vasodilatory septic shock	• **Shock:** ACCM/PALS guidelines definition • **FRSS:** after 30 ml/kg crystalloids	Not reported	12 pts	**Norepinephrine** (range 0.05 – 0.3 mcg/kg/min)	Not reported	Range 2 mo – 16 yrs	/	*Mortality:* 2 pts (15.4%)	
Rivero-Calle, 2016[5]	Retrospective Cohort Study	Single-center, 2008 – 2013, Spain (HIC)	<15 yrs with confirmed or probable invasive meningococcal disease diagnosis	• Not reported	Not reported	93 pts	**Dopamine** (range not reported)	Not reported	/	/	*Mortality*: 1 pt (1.1%)	*Time requiring vasoactive:* 2 (1-2) days, median IQR
Mc-Intosh, 2017[6]	Retrospective Cohort Study	Single-center, 2012 – 2015, USA (HIC)	> 2 mo, < 18 yrs patients with sepsis identified in the ED	• Not reported	Within 48 hours after arrival to the ED or ICU (not reported specifically)	70 pts	**Dopamine** (range 2 – 18 mcg/kg/min) not specified duration	Not specified	8.8 (4.7 - 13.4) yrs, median (IQR)	*ECMO:* 1 patient	*30-day mortality* 4 pts (5.7%)	*Vasopressor days:* 2 (1-3) days, median (IQR) *Ventilator days:* 0 (0-3) median (IQR) *Hospital LOS:* 7 (4-12) days, median (IQR)
						22 pts	**Norepinephrine** (range 0.03 – 0.2 mcg/kg/min) not specified duration	Not specified	6.7 (12.8 – 16.2) yrs, median (IQR)	/	*30-day mortality* 0 pts (0%)	*Vasopressor days:* 2 (1-3) days, median (IQR) *Ventilator days:* 0 (0-1) days, median (IQR) *Hospital LOS:* 6 (5-12) days, median (IQR)
Menon, 2017[7]	RCT	Multi-center, 2014 – 2016, Canada (HIC)	Newborn (>38 GA), < 18 yrs patients with septic shock	• **Septic shock:** as cardiovascular instability, requiring the administration of at least one vasoactive medication, which in the opinion of the treating physician was not attributable to a hemorrhagic, hypovolemic, cardiogenic, or neurogenic/spinal pathology	Not reported	13 pts	**Dopamine** (range 2 – 15 mcg/kg/min)	Not specifically reported, suggested management as per SSC guidelines	/	*MV:* 8 pts (62%)	*Mortality:* 0 pts (0%)	/
						7 pts	**Epinephrine** (range 0.01 – 0.1 mcg/kg/min)			*MV:* 5 pts (71%)	*Mortality:* 1 pts (14%)	/
						6 pts	**Norepinephrine** (range 0.02 – 0.2 mcg/kg/min)			*MV:* 4 pts (66%)	*Mortality:* 0 pts (0%)	/
Kohn-Loncarica, 2020[8]	Retrospective Cohort Study	Single-center, 2009 – 2017, Argentina (UMIC)	Children with FRSS admitted to the PED	• **Septic shock:** children admitted to PED with fever, tachycardia, and suspicion of infection associated with signs of tissue hypoperfusion. • **FRSS:** infusion of 60 mL/kg of fluids or clinical signs of fluid overload or poor general status	Not reported	69 pts	**Dopamine** (range not reported)	According to ACCM guidelines	81 (31–144) mo, median (IQR)	*MV:* 28 pts (40.6%)	*Mortality:* 9 pts (13.0%)	*Duration of MV:* 5.5 days, IQR not reported *ICU LOS:* 4 days, IQR not reported *Hospital LOS:* 13 days, IQR not reported
						49 pts	**Epinephrine** (range not reported)	According to ACCM guidelines	63 (19–92) mo, median (IQR)	*MV:* 19 pts (38.8%)	*Mortality:* 5 pts (10.2%)	*Duration of MV:* 4 days, IQR not reported *ICU LOS:* 4 days, IQR not reported *Hospital LOS:* 11 days, IQR not reported

Chowdhury, 2022[9]	Retrospective Cohort Study	Single-center, 2013 – 2017, Bangladesh (LMIC)	2 – 59 mo malnourished patients with FRSS admitted to the PICU that received a blood transfusion for unresponsiveness to crystalloids	• **FRSS:** tachycardia, with hypo or hyperthermia, or abnormal white blood cell (WBC) count were present, along with the presumed presence of infection, with age-specific hypotension that did not resolve with 20 mL/kg - maximum of 40 mL/kg	Not reported	25 pts	**Dopamine** (range not reported)	No clinical improvement, followed by epinephrine initiation	Range 2–59 mo	/	*Mortality:* 6 pts (24.0%)	*Shock resolution:* 19 pts (76%)
Iramain, 2022[10]	RCT	Multi-center, 2015-2020 Colombia (UMIC)	<18 yrs patients with hypotensive septic shock at PED admission	• **Septic shock:** defined according to ACCM and SSC guidelines • **FRSS:** patients with minimal or no signs of improvement or patients with signs of fluid overload after 40 mL/kg (up to 60 mL/kg in one of the arms of the study)	After 40 mL/kg of fluid (first arm), after 60 mL/kg (second arm)	63 pts	**Epinephrine** (0.1 mcg/kg/min – upper range not reported)	Not reported	Not reported for the whole cohort	*MV:* 15 pts (23.8%)	*Mortality:* 14 pts (22.2%)	/
Kohn-Loncarica, 2022[11]	Prospective Cohort Study	Single-center, 2015 - 2018, Argentina (UMIC)	1 mo – 16 yrs patients with septic shock admitted to the PED and requiring PVL administration of inotropic drug	• **Septic shock:** ACMM guidelines. • **FRSS:** infusion of 40 to 60 mL/kg of fluids or more; or appearance of clinical signs of fluid overload; or presence of "critical condition" (hypotension, or restlessness, or sensory depression, or cyanotic/mottled skin appearance	After 30 minutes of resuscitation according to ACCM guidelines and not achieving clinical goals	33 pts	**Epinephrine** (range 0.05 – 0.3 mcg/kg/min)	Not reported	6 (2–11.8) yrs, median (IQR)	/	*Mortality:* 1 pt (3.0%)	*Time requiring vasopressors:* 24 (0-48) hours, median (IQR) *ICU LOS:* 4.5 (3-7) days, median (IQR) *Hospital LOS:* 8 (7-14.5) days, median (IQR)
						6 pts	**Norepinephrine** (range 0.05 – 1.0 mcg/kg/min)	Not reported		/	*Mortality:* 0 pts (0.0%)	*Time requiring vasopressors:* 36 (24-72) hours, median (IQR) *ICU LOS:* 4 (1.75-9.5) days, median (IQR) *Hospital LOS:* 17.5 (9.25-32.75) days, median (IQR)
Banothu, 2023[12]	RCT	Single-center, India (LMIC)	> 2 mo, < 18 yrs patients with cold FRSS	• **Septic shock:** children with suspected infection and at least two signs of decreased perfusion with or without hypotension • **FRSS (vasoconstricted "cold" shock):** signs of cold shock and poor perfusion despite 40 mL/kg of fluid bolus or if there was worsening after fluid therapy	After randomization – not reported timing	33 pts	**Epinephrine** (0.1-0.3 mcg/kg/min, as >0.3 were labeled as treatment refractory)	In children who failed to attain therapeutic end-points, epinephrine dose was titrated every 15 minutes, up until 0.3 mcg/kg/min (treatment refractory), following management as per ACCM guidelines	5 (1.5–10) yrs, median (IQR)	*Other vasoactive:* 27 pts (82%) *MV:* 28 pts (85%) *Hydrocortisone:* 15 pts (44%) *RRT:* 9 pts (27.2%)	*28-day Mortality:* 13 pts (39.3%)	*Shock resolution (at 1 hour):* 3 pts (9%) *Shock resolution (at 6 hours):* 18 pts (54.5%) *Shock resolution (at 24 hours):* 28 pts (84.8%) *Time to shock resolution:* 6 (3-10) hours, median (IQR) *Duration of vasoactive therapy:* 65 (40-124) hours, median (IQR) *Duration of MV:* 6.5 (3.2-19) days, median (IQR) *Duration of PICU stay:* 6 (5-13) days, median (IQR) *Duration of hospital stay:* 15 (9-28) days, median (IQR) *SOFA day 3:* 8 (5-10), median (IQR)

Abbreviations: ACCM, American College of Critical Care Medicine; ECMO, Extracorporeal-Membrane Oxygenation; FRSS, Fluid-Refractory Septic Shock; GA, Gestational Age; HIC, High-Income Country; IQR, Interquartile Range; LMIC, Lower-Middle Income Country; mo, months; MV, Mechanical Ventilation; PALS, Pediatric Advanced Life Support; PED, Pediatric Emergency Department; PICU, Pediatric Intensive Care Unit; PVL, Peripheral venous line; pts, patients; RCT, Randomized Clinical Trial; RRT, renal replacement therapy; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; UMIC, Upper-Middle Income Country; yrs, years; wks, weeks.

Table S4. Studies reporting outcomes on patient undergoing 2 vasoactive agents for FRSS

First Author, Year	Study Design	Single vs Multi-center, Study Period, Country	Inclusion Criteria	Definitions of Sepsis, Septic Shock & FRSS ("trigger to vasoactive")	Trigger-To-Vasoactive	N. of Patients on 1 Vasoactive Agent	Vasoactive Received (Drug, Dosage, Duration)	Reason for change / escalation to more vasoactives	Age (cohort)	Adjunctive Therapies	Mortality Rate (Primary Outcome)	Secondary Outcomes
Plotz FB, 2005[13]	Retrospective Cohort Study,	Single-center, 1998 – 2004, Netherlands (HIC)	>28 days with fluid-refractory dopamine-resistant septic shock,	• Not reported	Not reported	22 pts	**Norepinephrine** (range not reported) **Dopamine** (range not reported)	Not reported	Range 2-172 mo	*RRT:* 7 patients (31.8%)	*Mortality:* 5 pts (22.7%)	/
Fernandez, 2016[2]	Retrospective Cohort Study	Single-center, 2008 – 2013, Colombia (UMIC)	1 mo – 18 yrs with crystalloid-refractory septic shock	• Not reported	Not reported	59 pts	**Norepinephrine** 1 mcg/kg/min **Vasopressin** (range 0.1 mcg/kg/min - ?) (maximum not reported)	Not reported	49 mo ± 59, mean ± SD	*Steroids:* 59 patients (100%)	*28-day mortality:* 34 pts (57.6%)	/
Ranjit, 2016[4]	Retrospective Cohort Study	Single-center, 2014 – 2015, India (LMIC)	1 mo – 16 yrs with fluid-refractory vasodilatory septic shock	• **Shock:** ACCM/PALS guidelines definition • **FRSS:** after 30 ml/kg crystalloids	Not reported	6 pts	**Norepinephrine** (range not reported) **Epinephrine** (range not reported)	Not reported	Range 2 mo – 16 yrs	/	*Mortality:* 0 pts (0%)	/
Rivero-Calle, 2016[5]	Retrospective Cohort Study	Single-center, 2008 – 2013, Spain (HIC)	<15 yrs with confirmed or probable invasive meningococcal disease diagnosis	• Not reported	Not reported	12 pts	**Dopamine** (range not reported) **Dobutamine** (range not reported)	Not reported	/	/	*Mortality:* 0 pts (0%)	/
						8 pts	**Dopamine** (range not reported) **Epinephrine** (range not reported)			/	*Mortality:* 0 pts (0%)	/
						24 pts	**Dopamine** (range not reported) **Norepinephrine** (range not reported)			/	*Mortality:* 0 pts (0%)	/
Mc-Intosh, 2017[6]	Retrospective Cohort Study	Single-center, 2012 – 2015, USA (HIC)	> 2 mo, < 18 yrs patients with sepsis identified in the ED	• Not reported	Within 48 hours after arrival to the ED or ICU (not reported specifically)	22 pts	**Dopamine** (range 3 – 20 mcg/kg/min) **Norepinephrine** (range 0.02 – 0.2 mcg/kg/min)	Not specified	9.1 (3.7 – 14.8) yrs, median (IQR)	/	*30-day mortality* 0 pts (0%)	*Vasopressor days:* 2 (2-3) days, median (IQR) *Ventilator days:* 0 (0-4) days, median (IQR) Hospital LOS: 9 (5-12) days, median (IQR)
						5 pts	**Dopamine** (range 3 – 15 mcg/kg/min) **Epinephrine** (range 0.02 – 0.4 mcg/kg/min)	Not specified	6.0 (5.0 – 6.0) yrs, median (IQR)	/	*30-day mortality* 0 pts (0%)	*Vasopressor days:* 3 (3-5) days, median (IQR) *Ventilator days:* 3 (0-5) days, median (IQR) *Hospital LOS:* 11 (9-23) days, median (IQR)
Menon, 2017[7]	RCT	Multi-center, 2014 – 2016, Canada (HIC)	Newborn (>38 GA), < 18 yrs patients with septic shock	• **Septic shock:** as cardiovascular instability, requiring the administration of at least one vasoactive medication, which in the opinion of the treating physician was not attributable to a hemorrhagic, hypovolemic, cardiogenic, or neurogenic/spinal pathology	Not reported	6 pts	**Dopamine** (range 7.5-12 mcg/kg/min) **Norepinephrine** (range 0.05-0.15 mcg/kg/min)	Not specifically reported, suggested management as per SSC guidelines	/	*MV:* 4 pts (66%)	*Mortality:* 0 pts (0%)	/
						8 pts	**Epinephrine** (range 0.1-1 mcg/kg/min) **Norepinephrine** (range 0.03-0.5 mcg/kg/min)			*MV:* 4 pts (50%) 1 pt needed ECMO support	*Mortality:* 1 pts (13%)	/
Chowdhury, 2022[9]	Retrospective Cohort Study	Single-center, 2013 – 2017, Bangladesh (LMIC)	2 – 59 mo malnourished patients with FRSS admitted to the PICU that received a blood transfusion for unresponsiveness to crystalloids	• **FRSS:** tachycardia, with hypo or hyperthermia, or abnormal white blood cell (WBC) count were present, along with the presumed presence of infection, with age-specific hypotension that did not resolve with 20 mL/kg - maximum of 40 mL/kg	Not reported	37 pts	**Dopamine** (range not reported) **Epinephrine** (range not reported)	Not reported	Range 2–59 mo	/	*Mortality:* 23 pts (62.2%)	*Shock resolution:* 14 pts (37.8%)

Kohn-Loncarica, 2022[11]	Prospective Cohort Study	Single-center, 2015 - 2018, Argentina (UMIC)	1 mo – 16 yrs patients with septic shock admitted to the PED and requiring PVL administration of inotropic drug	• **Septic shock:** ACMM guidelines. • **FRSS:** infusion of 40 to 60 mL/kg of fluids or more; or appearance of clinical signs of fluid overload; or presence of "critical condition" (hypotension, or restlessness, or sensory depression, or cyanotic/mottled skin appearance	After 30 minutes of resuscitation according to ACCM guidelines and not achieving clinical goals	6 pts	**Epinephrine** (range not reported) **Norepinephrine** (range not reported)	Not reported	6 (2–11.8) yrs, median (IQR)	/	*Mortality:* 0 pts (0.0%)	*Time requiring vasopressors*: 48 (18-60) hours, median (IQR) *ICU LOS:* 4 (2-6.5) days, median (IQR) *Hospital LOS:* 12 (5-27.75) days, median (IQR)
Banothu, 2023[12]	RCT	Single-center, India (LMIC)	> 2 mo, < 18 yrs patients with cold FRSS	• **Septic shock:** children with suspected infection and at least two signs of decreased perfusion with or without hypotension • **FRSS (vasoconstricted "cold" shock):** signs of cold shock and poor perfusion despite 40 mL/kg of fluid bolus or if there was worsening after fluid therapy	After randomization – not reported timing	34 pts	**Norepinephrine** **Dobutamine**	In children who failed to attain therapeutic end-points, vasoactive agents were titrated as per the physiologic status. In children with low blood pressure, norepinephrine dose was increased (up to 0.3 µg/kg/min), while in children with normal blood pressure and signs of poor perfusion, dobutamine was increased (20 µg/kg/min), , following management (treatment refractory) as per ACCM guidelines	7.5 (3–10) yrs, median (IQR)	*Other vasoactive:* 10 pts (29.4%) *MV:* 23 pts (68%) *Hydrocortisone:* 15 pts (45%) *RRT:* 7 pts (20.5%)	*28-day Mortality:* 8 pts (23.5%)	*Shock resolution (at 1 hour):* 6 pts (17.6%) *Shock resolution (at 6 hours):* 26 pts (76.4%) *Shock resolution (at 24 hours):* 33 pts (97.1%) *Time to shock resolution: 3* (2-6) hours, median (IQR) *Duration of vasoactive therapy: 52* (25-146) hours, median (IQR) *Duration of MV: 8* (6-12) days, median (IQR) *Duration of PICU stay: 10* (6-14) days, median (IQR) *Duration of hospital stay:* 19 (10-29) days, median (IQR) *SOFA day 3:* 6 (3-10), median (IQR)

Abbreviations: ACCM, American College of Critical Care Medicine; ECMO, Extracorporeal-Membrane Oxygenation; FRSS, Fluid-Refractory Septic Shock; GA, Gestational Age; HIC, High-Income Country; IQR, Interquartile Range; LMIC, Lower-Middle Income Country; mo, months; MV, Mechanical Ventilation; PALS, Pediatric Advanced Life Support; PED, Pediatric Emergency Department; PICU, Pediatric Intensive Care Unit; PVL, Peripheral venous line; pts, patients; RCT, Randomized Clinical Trial; RRT, renal replacement therapy; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; UMIC, Upper-Middle Income Country; yrs, years; wks, weeks.

Table S5. Distribution of reporting of Secondary Outcomes across the included studies

Studies		1	2	3	4	5	6	7	8	9	10	11	12	13
Secondary Outcomes	**N° Studies**	**Plotz**	**Ventura**	**Fernan-dez**	**Ramas-wamy**	**Ranjit**	**Rivero-Calle**	**Mc-Intosh**	**Menon**	**Kohn-Loncarica (2020)**	**Chowd-hury**	**Iramain**	**Kohn-Loncarica (2022)**	**Banothu**
Shock and vasoactives														
Resolution of shock (overall)	3				1						1			1
Resolution of shock at certain time	2				1									1
Time to shock resolution	1													1
Duration of vasoactives therapy	4						1	1					1	1
Need for other vasoactive	2		1											1
Need for steroids	3		1		1									1
Mechanical Ventilation (MV)														
Need for mechanical ventilation (MV)	5		1		1				1	1				1
Duration of MV	4				1			1		1				1
Other organ support			1											
Need for renal replacement therapy (RRT)	2	1												1
Need for ECLS	0													
Length of Stays (LOS)														
Hospital LOS	5				1			1		1			1	1
ICU LOS	4				1					1			1	1
Free-Days														
Ventilatory-free days	1		1											
Vasoactive drug-free days	1		1											
Organ failure free days	1				1									
SOFA														
SOFA day 1	1													1
SOFA day 2	1													1
SOFA day 3	2				1									1

Table S6A. Quality assessment for randomized controlled trials on the primary outcome / Mortality (RoB 2)

Questions' domains:
Domain 1: Risk of bias arising from the randomization process
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Domain 3: Risk of bias due to missing outcome data
Domain 4: Risk of bias in measurement of the outcome
Domain 5: Risk of bias in selection of the reported result

Study		RoB arising from the randomization process			RoB J.	RoB due to deviations from the intended interventions (effect of assignment to intervention)							RoB J.
Author	Year	Q1.1	Q1.2	Q1.3		Q2.1	Q2.2	Q2.3	Q2.4	Q2.5	Q2.6	Q2.7	
Ventura	2015	Y	Y	N	Low risk	N	N	NA	NA	NA	Y	NA	Low risk
Ramaswamy	2016	Y	Y	N	Low risk	N	N	NA	NA	NA	Y	NA	Low risk
Menon	2017	Y	Y	N	Low risk	N	N	NA	NA	NA	PY	NA	Low risk
Iramain	2022	N	NI	PN	Some concerns	PN	Y	NI	NI	NI	PY	NA	Some concerns
Banothu	2023	Y	Y	N	Low risk	PN	Y	PN	NA	NA	Y	NA	Low risk

Study		RoB due to missing outcome data				RoB J.	RoB in measurement of the outcome					RoB J.	RoB in selection of the reported result			RoB J.	Overall RoB J.
Author	Year	Q3.1	Q3.2	Q3.3	Q3.4		Q4.1	Q4.2	Q4.3	Q4.4	Q4.5		Q5.1	Q5.2	Q5.3		
Ventura	2015	Y	NA	NA	NA	Low risk	N	N	NA	NA	NA	Low risk	Y	N	N	Low risk	Low risk
Ramaswamy	2016	Y	NA	NA	NA	Low risk	N	N	NA	NA	NA	Low risk	Y	N	N	Low risk	Low risk
Menon	2017	N	N	PY	PN	Some concerns	N	N	PY	PN	NI	Low risk	NI	N	PN	Some concerns	High risk
Iramain	2022	PY	NA	NA	NA	Low risk	N	N	Y	N	N	Low risk	PY	N	N	Low risk	High risk
Banothu	2023	Y	NA	NA	NA	Low risk	N	N	Y	N	N	Low risk	Y	N	N	Low risk	Low Risk

Abbreviations: RoB J.: Risk-of-Bias Judgement; Y: Yes; N: No; NA: Not Applicable; NI: No Information; PN: Probably No; PY: Probably Yes.

Table S6B. Quality assessment for the observational studies on the primary outcome / Mortality (Newcastle-Ottawa scale)

Study			Selection				Comparability	Outcome			Total Score (9★/9★)	Interpretation on quality
Author	Year	Type	Representative of the exposed cohort	Selection of external cohort	Asceirtain-ment of exposure	Outcome of interest not present at the start of the study		Assessment of outcomes	Sufficient follow-up time	Adequacy of follow-up		
Plotz	2005	CS	★	NA[a]	★	★	NA[b]	★	★	★	6/9 ★★★★★★	Fair
Mc-Intosh	2015	CS	★	NA[a]	★	★	NA[b]	0[d]	★	★	5/9 ★★★★★	Fair
Fernandez	2016	CS	★	NA[a]	★	★	★	★	★	★	8/9 ★★★★★★★★	Strong
Ranjit	2016	CS	★	NA[a]	★	★	NA[b]	0[d]	★	★	5/9 ★★★★★	Fair
Rivero-Calle	2016	CS	0	0	0[c]	★	NA[b]	0[d]	★	★	3/9 ★★★	Poor
Kohn-Loncarica (retrospective)	2020	CS	★	NA[a]	★	★	★	★	★	★	8/9 ★★★★★★★★	Strong
Kohn-Loncarica (prospective)	2020	CS	★	NA[a]	★	★	NA[b]	0[d]	★	★	5/9 ★★★★★	Fair
Chowdhury	2022	CC	★	NA[a]	★	★	NA[b]	0[d]	★	★	5/9 ★★★★★	Fair

Judgment: <5 Poor; 5-7 Fair; 8-9 Strong

Abbreviations: CC: Case Control; CS: Cohort Study; NA: Not Applicable
[a] All patients were exposed to vasoactives
[b] No comparison among different vasoactives performed in the study
[c] All the studies where the exposure to specific vasoactives was retrieved by personal correspondence received zero in this field (as data was not peer-reviewed)
[d] All the studies where the primary outcome according to specific vasoactives was retrieved by personal correspondence received zero in this field (as data was not peer-reviewed)

Comments:

As for RCTs, we judged three out of five trials to be at low RoB according to the Revised Cochrane RoB tool. Iramain et al. was rated as high RoB due to some concerns regarding the randomization process and the unblinding of the intervention. Menon et al. was rated as a high RoB study as the exposure to vasoactive drugs and the outcomes according to the single vasoactive were retrieved by personal correspondence. For those reasons, both studies were judged as low quality for the purpose of this review.

All but one of the observational cohort studies showed fair or high quality (score > 5/9) on each assessment area (selection, comparability, outcome) according to the Newcastle-Ottawa Scale (NOS). Rivero Calle et al. was the only study which was judged of low quality as it was unclear if the patients were representative of the target of this review and both exposure and outcomes related to single vasoactive drug were retrieved by personal correspondence.

Figures

Subgroup Analyses

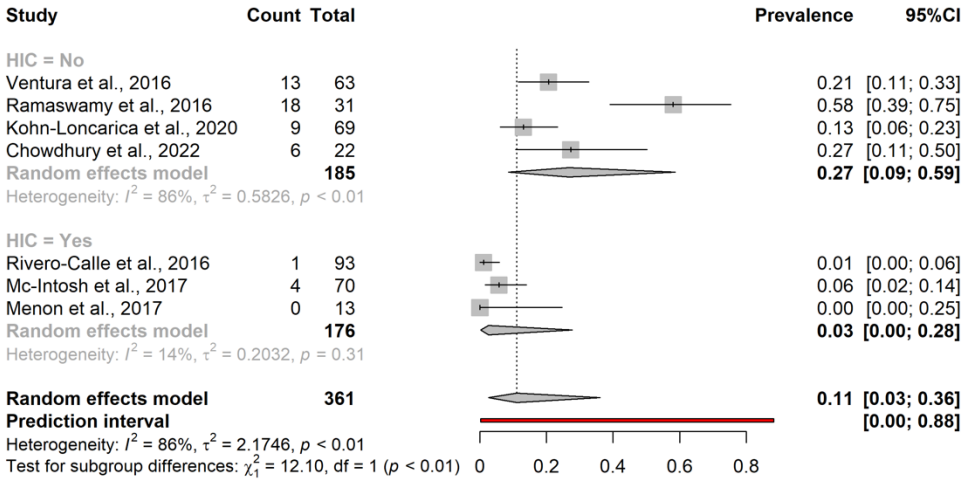

Figure S7.1 Mortality pooled estimate from studies on patients undergoing dopamine as first-line agent: HIC vs UMIC/LMICs subgroup analysis

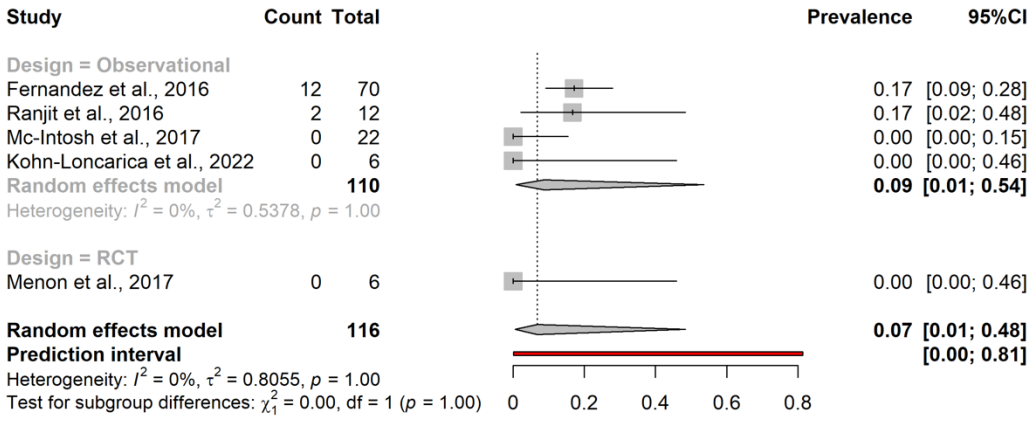

Figure S7.2 Mortality pooled estimate from studies on patients undergoing norepinephrine as first-line agent: OCSs vs RCTs subgroup analysis.

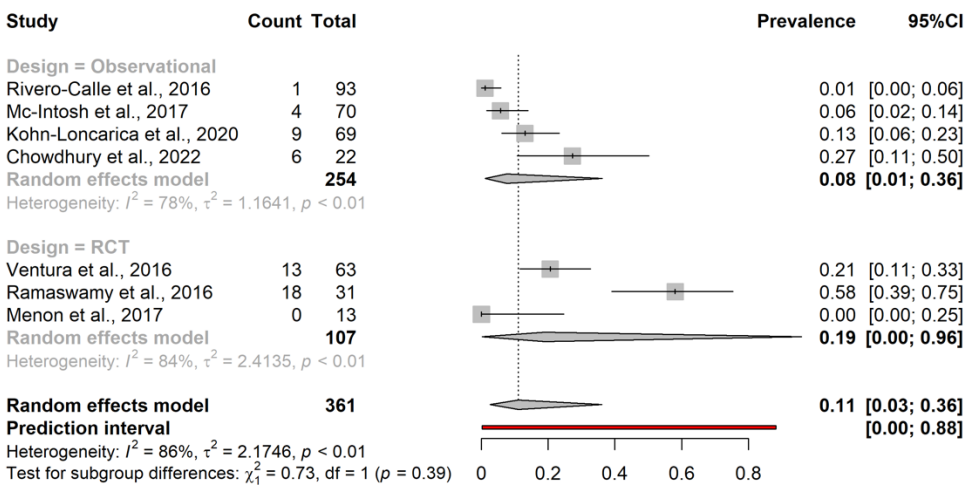

Figure S7.3 Mortality pooled estimate from studies on patients undergoing dopamine as first-line agent: OCSs vs RCTs subgroup analysis.

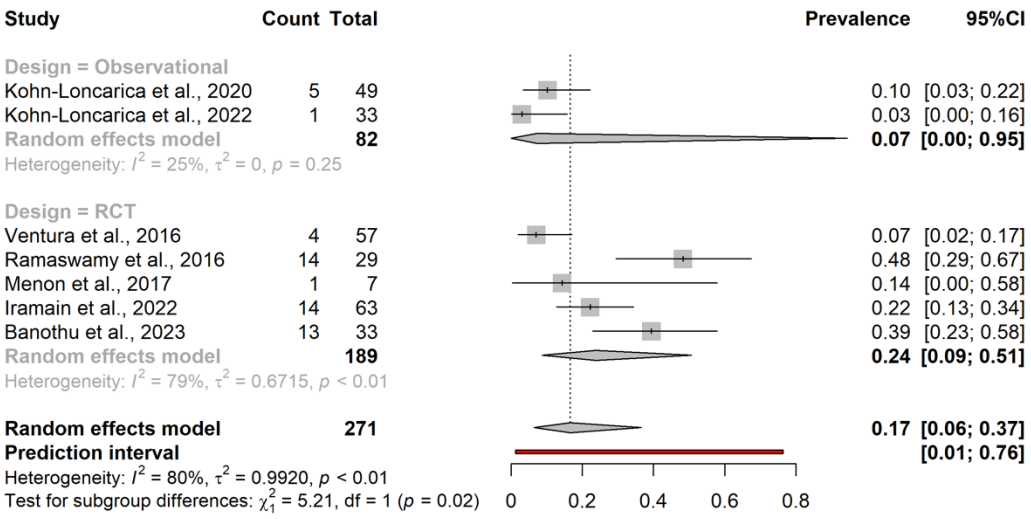

Figure S7.4 Mortality pooled estimate from studies on patients undergoing epinephrine as first-line agent: OCSs vs RCTs subgroup analysis.

Publication Bias and Sensitivity Analyses

Publication Bias

Table S8.1 Eggers' test

	p
Mortality Dopamine	0.215
Mortality Epinephrine	0.183
Mortality Norepinephrine	0.078
Mortality dopa vs epi	0.845
MV dopa vs epi	0.967

Funnel Plots

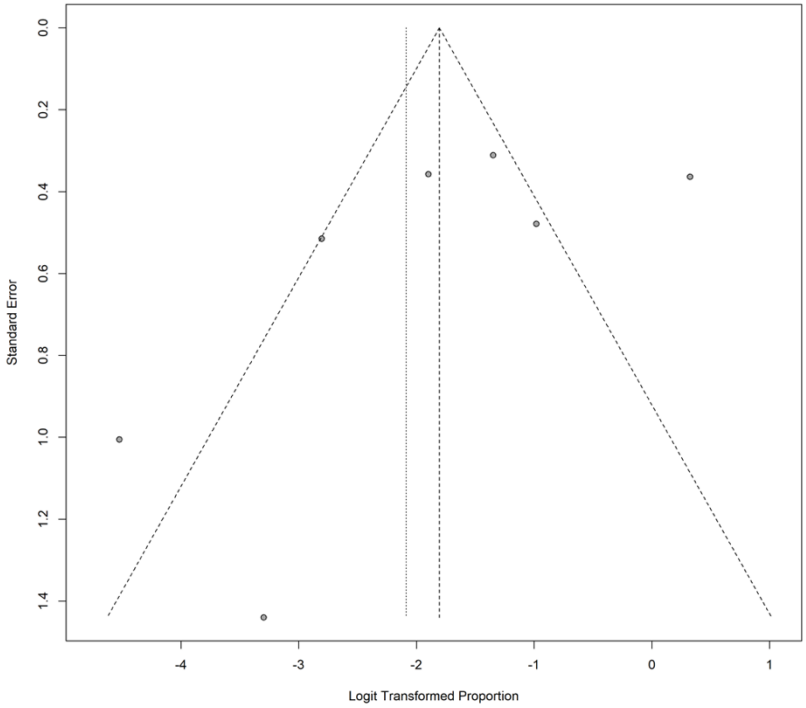

Figure S8.1 Funnel plot of the studies on mortality in patients undergoing dopamine as first-line vasoactive agent.

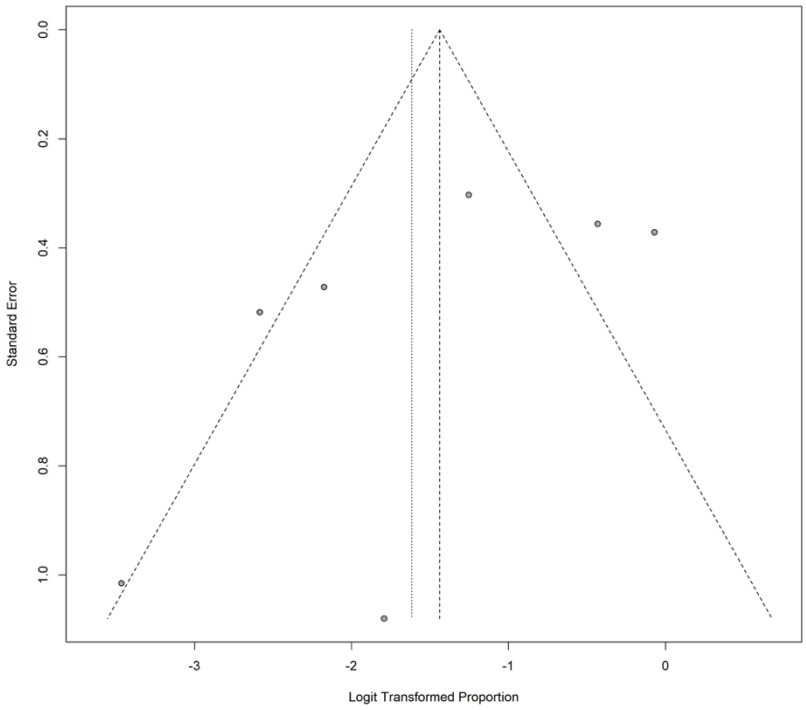

Figure S8.2 Funnel plot of the studies on mortality in patients undergoing epinephrine as first-line vasoactive agent.

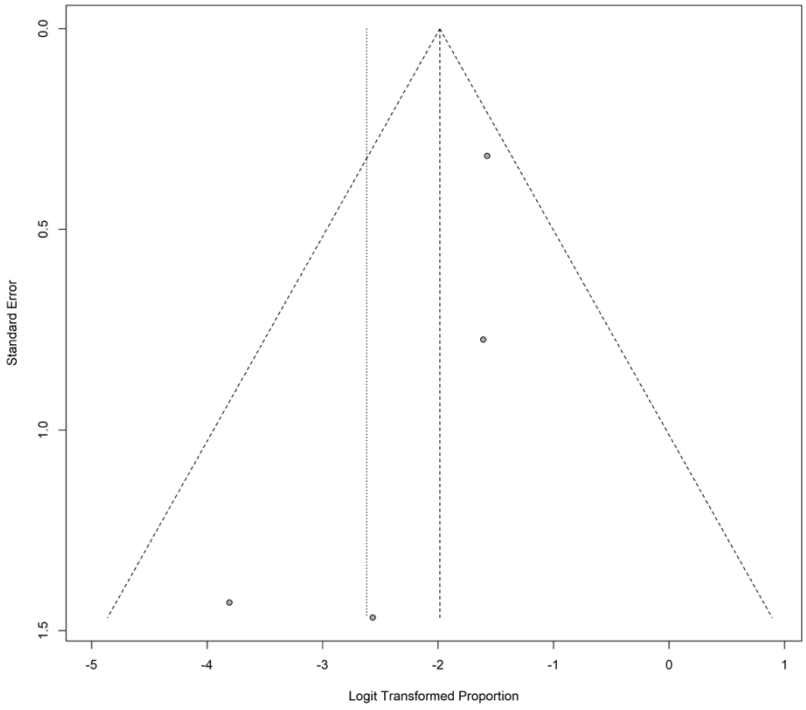

Figure S8.3 Funnel plot of the studies on mortality in patients undergoing norepinephrine as first-line vasoactive agent.

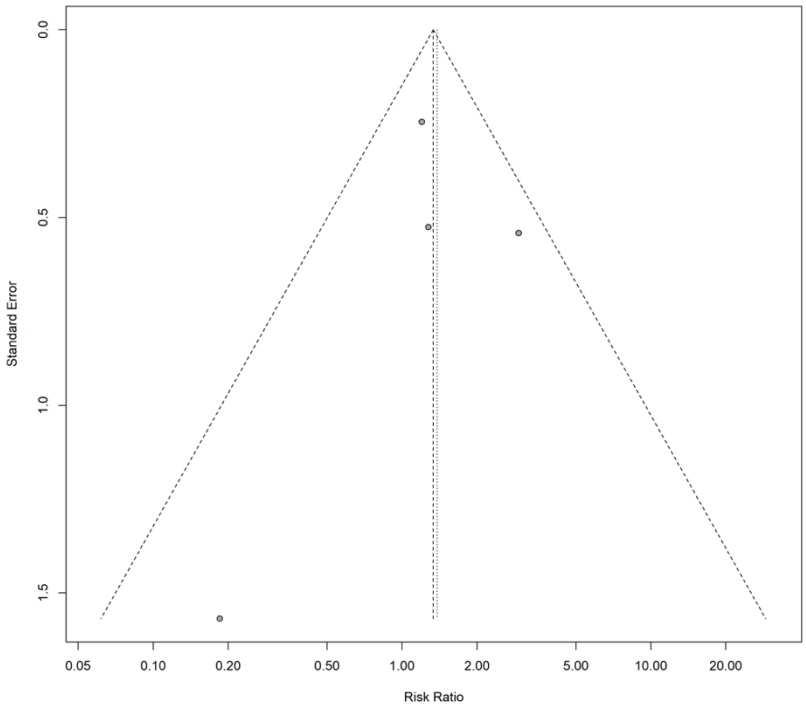

Figure S8.4 Funnel plot of the studies on mortality in the comparison between dopamine and epinephrine as first-line vasoactive agent.

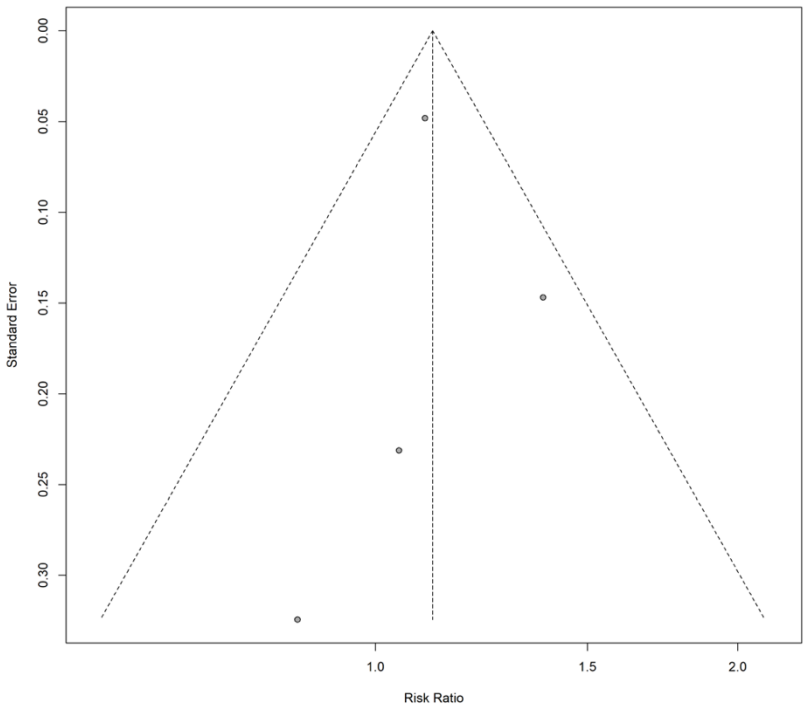

Figure S8.5 Funnel plot of the studies including the comparison between dopamine and epinephrine as first-line vasoactive agent on need for MV.

Sensitivity analyses

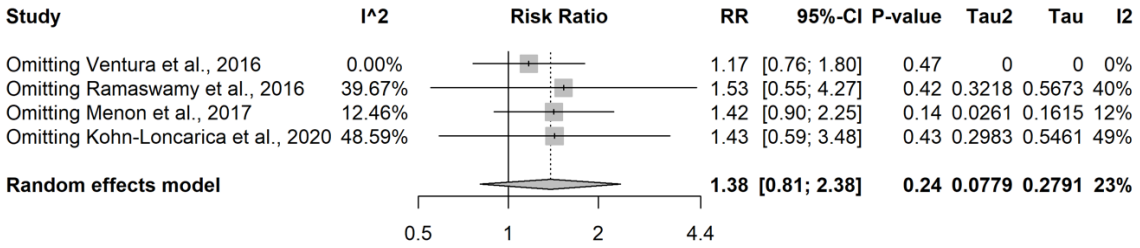

Figure S8.6 Mortality: leave-one-out analysis of studies comparing patients undergoing dopamine vs epinephrine as first-line vasoactive agent.

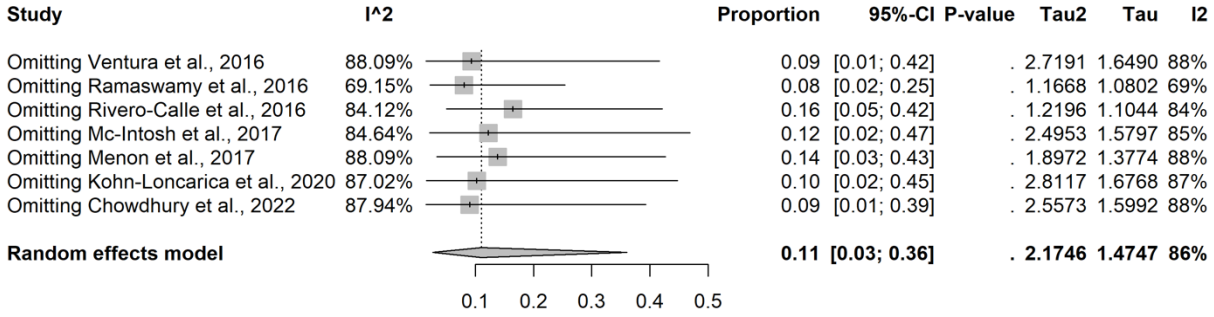

Figure S8.7 Mortality: leave-one-out analysis of studies on patients undergoing dopamine as first-line vasoactive agent.

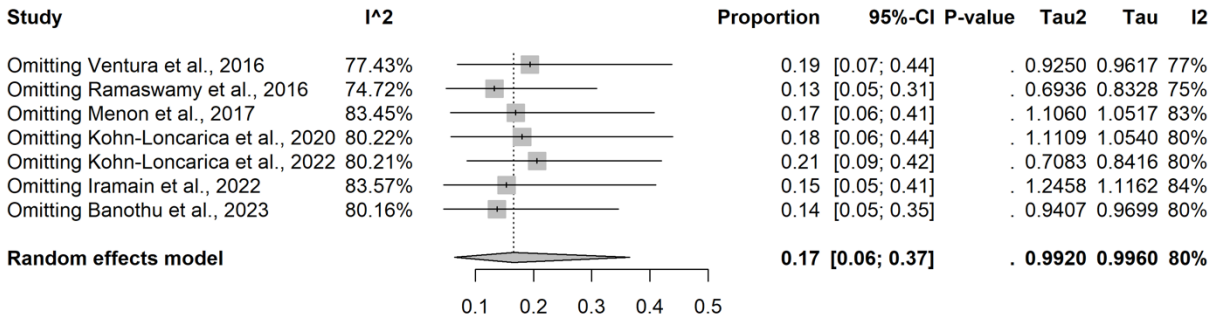

Figure S8.8 Mortality: leave-one-out analysis of studies on patients undergoing epinephrine as first-line vasoactive agent.

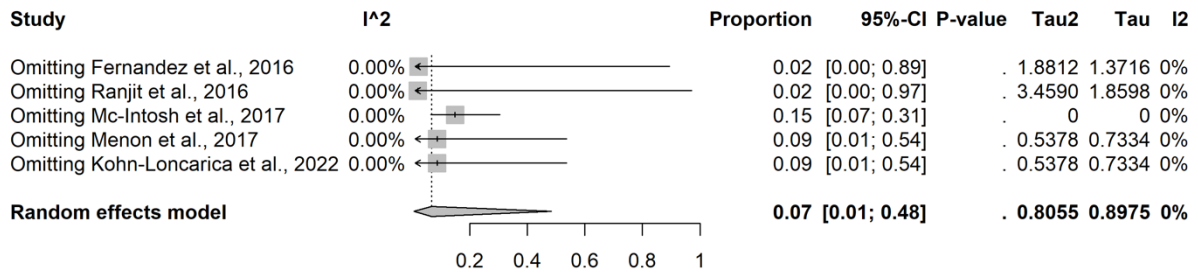

Figure S8.9 Mortality: leave-one-out analysis of studies on patients undergoing norepinephrine as first-line vasoactive agent.

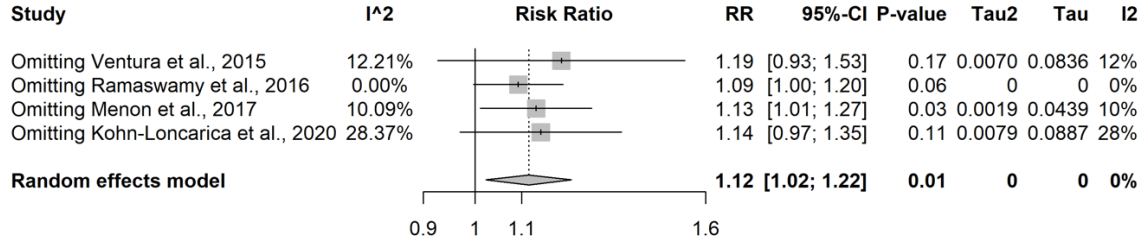

Figure S8.10 Need for MV: leave-one-out analysis of studies comparing the use of dopamine vs epinephrine as first-line vasoactive agent.

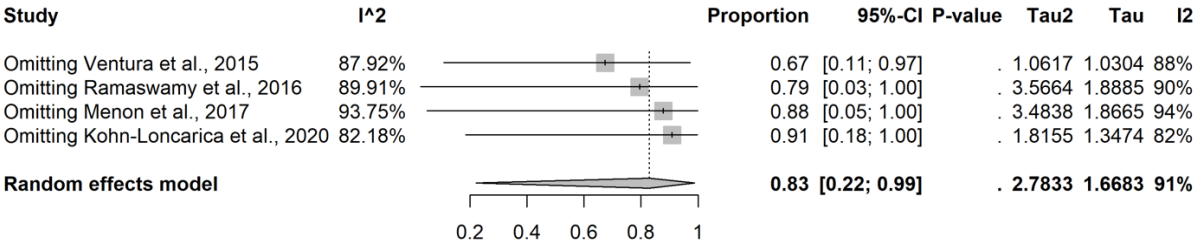

Figure S8.11 Need for MV: leave-one-out analysis of studies on patients undergoing dopamine as first-line vasoactive agent.

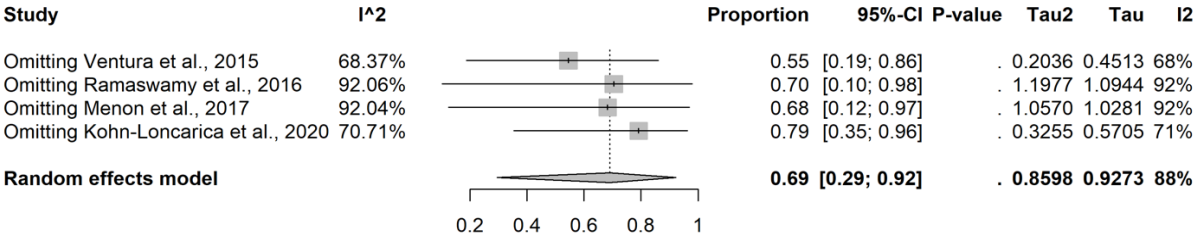

Figure S8.12 Need for MV: leave-one-out analysis of studies on patients undergoing epinephrine as first-line vasoactive agent.

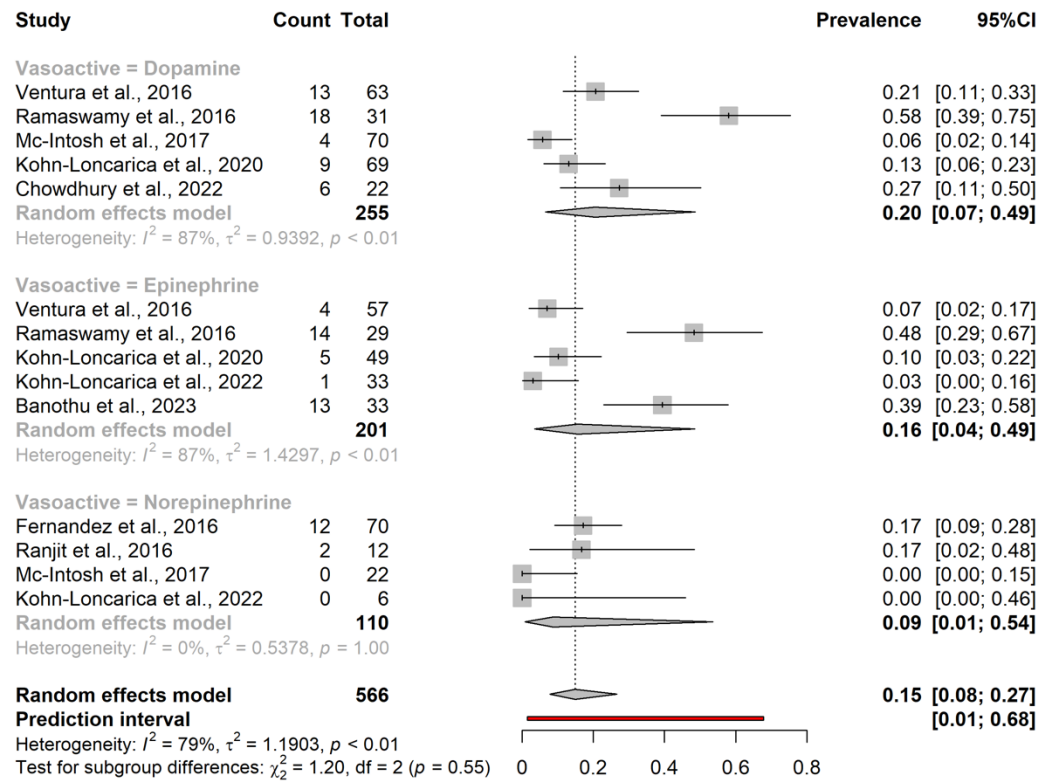

Figure S8.13 Mortality: sensitivity analysis of studies on patients undergoing dopamine, epinephrine and norepinephrine as first-line vasoactive agent, excluding low-quality studies.

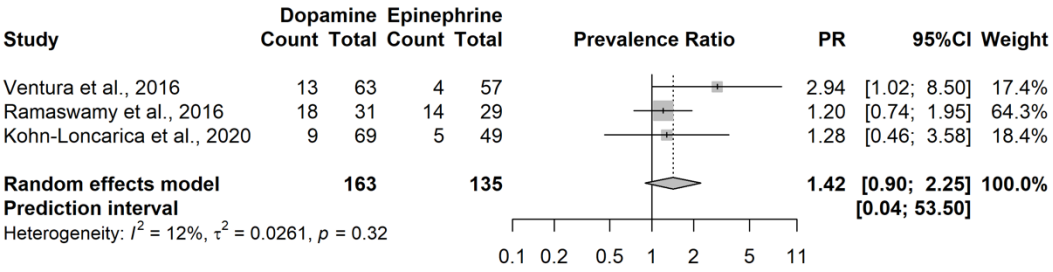

Figure S8.14 Mortality: sensitivity analysis of studies comparing the use of dopamine vs epinephrine as first-line vasoactive agent, excluding low-quality studies.

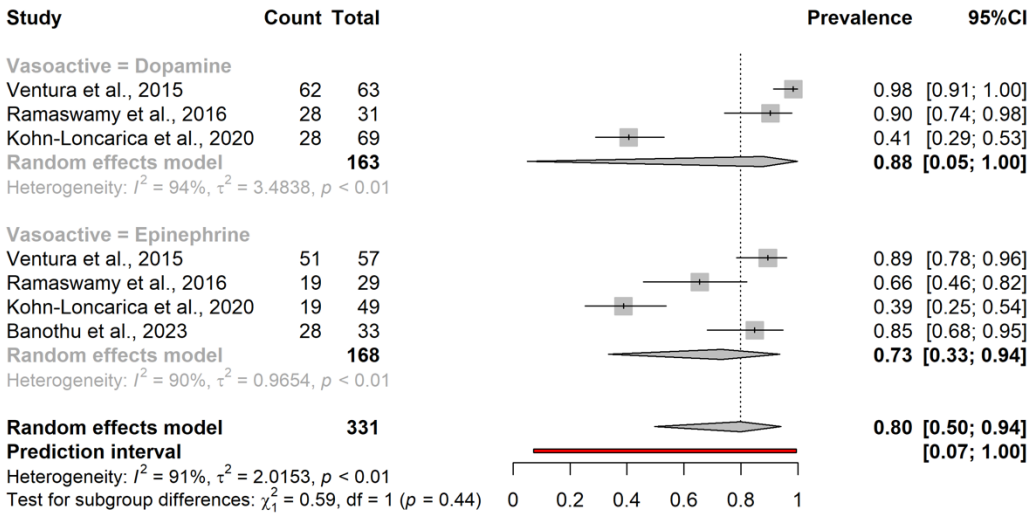

Figure S8.15 Need for MV: sensitivity analysis of studies on patients undergoing dopamine, epinephrine and norepinephrine as first-line vasoactive agent, excluding low-quality studies.

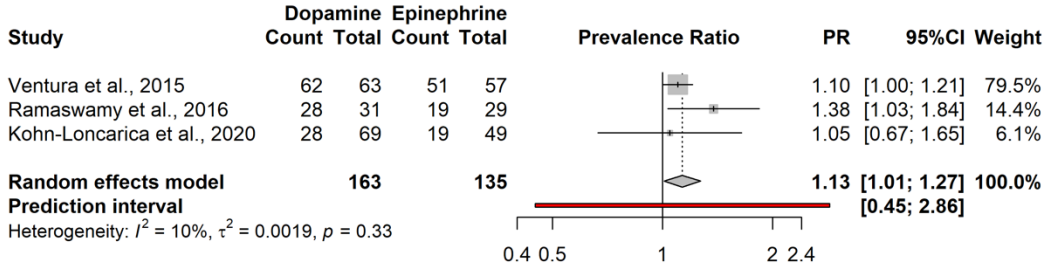

Figure S8.16 Need for MV: sensitivity analysis of studies comparing the use of dopamine vs epinephrine as first-line vasoactive agent, excluding low-quality studies.

PRISMA Checklist

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist

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You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Section/Topic	Item No.	Checklist item	Reported on Page No.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	

Section/Topic	Item No.	Checklist item	Reported on Page No.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			

Section/Topic	Item No.	Checklist item	Reported on Page No.
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Once you have completed this checklist, please save a copy and upload it as part of your submission. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

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Supplementary Content – Appendix 2

Sepsis prognostic scores accuracy in predicting adverse outcomes in children with sepsis admitted to the PICU from the Emergency Department: a 10-year single-center experience

Luca Marchetto, MD[1,2,3] Rosanna Comoretto, PhD[4,5] Dario Gregori, PhD[4] Liviana Da Dalt, MD[6] Angela Amigoni A., MD[1] Marco Daverio, MD, PhD[1]

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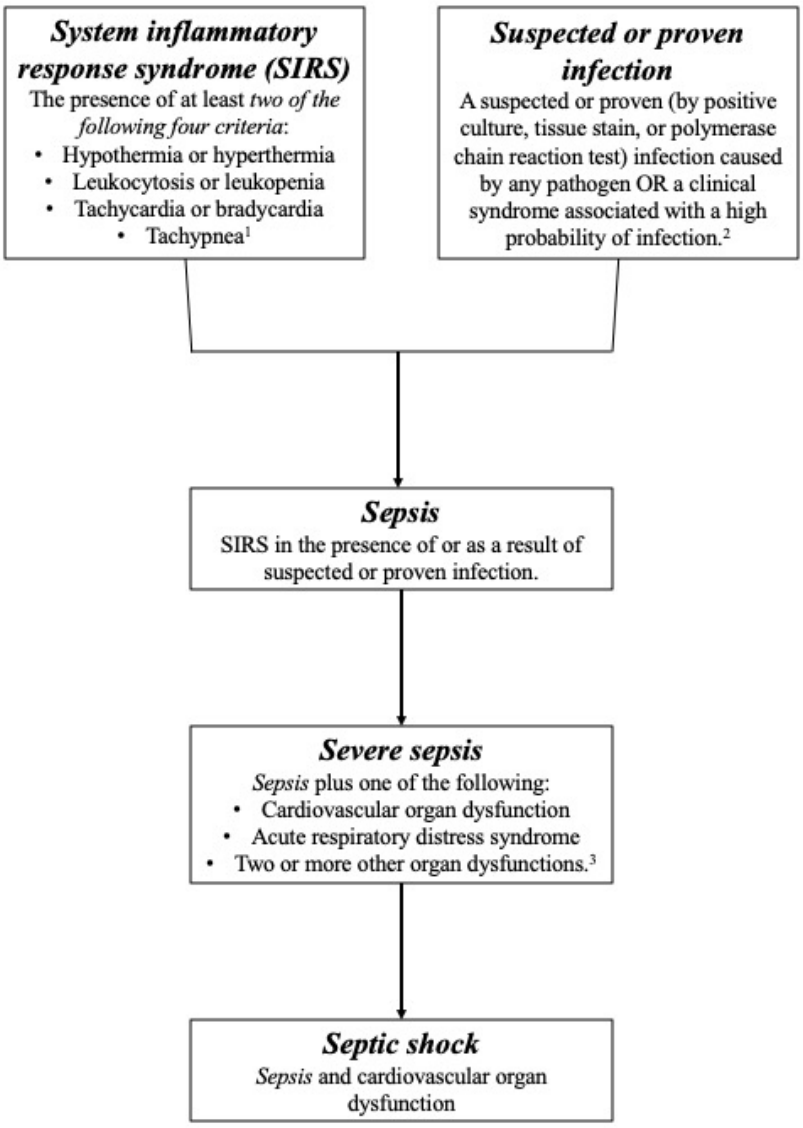
Predictive value of prognostic and diagnostic scores performed in the first 48 hours in critically ill children admitted to PICU with infection: a multi-center cohort prospective study

Preliminary results

International Consensus Conference on Pediatric Sepsis (ICCPS) definitions

Figure e1. Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock in the pediatric patient.



[1] Please see Table e1 for definition of SIRS and age-specific vital signs
[2] Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)
[3] Please see Table e2 for definition or organ dysfunctions
(Adapted from Goldstein B, Giroir B, Randolph A, et al.; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8)

Table e1. Pediatric SIRS Criteria (≥1 of the criteria from Column 1 AND Column 2)

	Column 1 (≥1 of the below criteria)			**Column 2 (≥1 of the below criteria)**			
	Heart rate		**Respiratory rate**	**White cell count[4]**		**Temperature[5]**	
	Beats per minute (bepm)		**Breaths per minute (brpm)**	**x $10^3/\mu$L**		**°C**	
Age group	**Tachycardia[1]**	**Bradycardia[2]**	**Tachypnea[3]**	**Leukocytosis**	**Leukopenia**	**Hypothermia**	**Hyperthermia**
0 days to 1 week	> 180	< 100	> 50	> 34	< 5	< 36	> 38.5
1 week to 1 month	> 180	< 100	> 40	> 19.5	< 5	< 36	> 38.5
1 month to 1 year	> 180	< 90	> 34	> 17.5	< 5	< 36	> 38.5
2 to 5 years	> 140	NA	> 22	> 15.5	< 6	< 36	> 38.5
6 to 12 years	> 130	NA	> 18	> 13.5	< 4.5	< 36	> 38.5
13 to <18 years	> 110	NA	> 14	> 11	< 4.5	< 36	> 38.5

[1] Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR for children <1-year-old.
[2] Bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, beta-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.
[2] Tachypnea, defined as a mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
[4] Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.
[5] Core temperature must be measured by rectal, bladder, oral, or central catheter probe.
(Adapted from Goldstein B, Giroir B, Randolph A, et al.; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8)

Table e2. Pediatric organ dysfunction criteria

<table>
<tr><td>Cardiovascular dysfunction (≥1 of the following despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 hr)</td><td>Neurologic (≥1 of the following)</td></tr>
<tr><td rowspan="3">Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age[1]
Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)
2 of the following
Unexplained metabolic acidosis: base deficit >5.0 mEq/L
Increased arterial lactate >2 times upper limit of normal
Oliguria: urine output <0.5 mL/kg/hr
Prolonged capillary refill: >5 secs
Core to peripheral temperature gap >3°C</td><td>Glasgow Coma Score ≤11
Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline</td></tr>
<tr><td>Hematologic (≥1 of the following)</td></tr>
<tr><td>Platelet count <80,000/mm3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)
INR >2</td></tr>
<tr><td>Respiratory[2] (≥1 of the following)</td><td>Renal</td></tr>
<tr><td rowspan="2">PaO_2/FIO_2 <300 in absence of cyanotic heart disease or preexisting lung disease
$PaCO_2$ >65 torr or 20 mm Hg over baseline $PaCO_2$
Proven need[3] or >50% FIO_2 to maintain saturation ≥92%
Need for non-elective invasive or noninvasive mechanical ventilation[4]</td><td>Serum creatinine ≥ 2 times upper limit of normal for age or 2-fold increase in baseline creatinine</td></tr>
<tr><td>Hepatic (≥1 of the following)</td></tr>
<tr><td></td><td>Total bilirubin ≥ 4 mg/dL (not applicable for newborn)
ALT 2 times upper limit of normal for age</td></tr>
</table>

[1] Please see Table e1;
[2] Acute respiratory distress syndrome must include a PaO_2/FIO_2 ratio 200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the PaO_2/FIO_2 ratio must be 300 mm Hg;
[3] Proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required;
[4] In postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.
(Adapted from Goldstein B, Giroir B, Randolph A, et al.; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8)

Prognostic scores

Table e3. Pediatric SOFA score

Reference	Variable	Age group	Points by severity levels				
			0	**1**	**2**	**3**	**4**
Respiratory							
Schlapbach et al.	**PaO_2(mmHg)/FiO_2**		≥ 400	300 - 399	200 - 299	100 - 199 respiratory support	< 100 with respiratory support
Matics and Sanchez-Pinto	**PaO_2(mmHg)/FiO_2**		≥ 400	300 - 399	200 - 299	100 - 199 with respiratory support	< 100 with respiratory support
	SpO_2/FiO_2		≥ 292	264 - 291	221 - 264	148 - 220 with respiratory support	< 148 with respiratory support
Shime et al.	**PaO_2(mmHg)/FiO_2**		> 400	≤ 400 with oxygen	≤ 300 with non-invasive ventilatory support	≤ 200 with ventilatory support	≤ 100 with ventilatory support
Coagulation							
Platelets ($x10^3/\mu L$)			≥ 150	100 - 149	50 - 99	20 - 49	< 20
Hepatic							
Bilirubin (μmol/L)			< 20	20 - 32	33 - 101	102 - 204	> 204
Cardiovascular							
Schlapbach et al.	**MAP (mmHg)**	< 2 years	≥ 60	44 - 59	31 - 43		≤ 30
		> 2 years to 5 years	≥ 62	46 - 61	32 - 44		≤ 31
		> 5 years to 12 years	≥ 65	49 - 64	36 - 48		≤ 35
		> 12 years to 18 years	≥ 67	52 - 66	38 - 51		≤ 37
		< 1 month	≥ 46	< 46			

Matics and Sanchez-Pinto	**MAP (mmHg) or vasoactive infusion (*μ*g/kg/min)**	> 1 month to 11 months	≥ 55	< 55	Dopamine ≤ 5or dobutamine at any day	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
		> 11 months to 23 months	≥ 60	< 60			
		> 24 months to 59 months	≥ 62	< 62			
		> 60 months to 143 months	≥ 65	< 65			
		> 144 months to 256 months	≥ 67	< 67			
Shime et al.	**SBP (mmHg) or vasoactive infusion (*μ*g/kg/min)**	< 1 week	≥ 60	< 60	Dopamine ≤ 5 or dobutamine at any dose	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
		> 1 week to 1 month	≥ 65	< 65			
		> 1 month to 2 years	≥ 70	< 70			
		> 2 years to 5 years	≥ 75	< 75			
		> 5 years to 12 years	≥ 80	< 80			
		> 12 years to 18 years	≥ 90	< 90			
Neurologic							
GCS			15	13 - 14	10 - 12	6 - 9	< 6
Renal							
Schlapbach et al.	**Creatinine (mg/dL)**	< 2 years	≤ 0.38		≥ 0.39		
		> 2 years to 5 years	≤ 0.56		≥ 0.57		
		> 5 years to 12 years	≤ 0.65		≥ 0.65		
		> 12 years to 18 years	≤ 1.04		≥ 1.05		
	Creatinine (mg/dL)	< 1 month	< 0.8	0.8 - 0.9	1.0 - 1.1	1.2 - 1.5	≥ 1.6

Matics and Sanchez-Pinto		> 1 month to 11 months	< 0.3	0.3 - 0.4	0.5 - 0.7	0.8 - 1.1	≥ 1.2
		> 11 months to 23 months	< 0.4	0.4-0.5	0.6 - 1.0	1.1 - 1.4	≥ 1.5
		> 24 months to 59 months	< 0.6	0.6 - 0.8	0.9 - 1.5	1.6 - 2.2	≥ 2.3
		> 60 months to 143 months	< 0.7	0.7 - 1.0	1.1 - 1.7	1.8 - 2.5	≥ 2.6
		> 144 months to 256 months	< 1.0	1.0 - 1.6	1.7 - 2.8	2.9 - 4.1	≥ 4.2
Shime et al.	**Creatinine (mg/dL)**	< 1 week	< 0.8	0.8 - 1.3	1.4 - 2.2	2.3 - 3.3	≥ 3.4
		> 1 week to 1 month	< 0.3	0.3 - 0.5	0.6 - 0.8	0.9 - 1.2	≥ 1.3
		> 1 month to 2 years	< 0.4	0.4 - 0.6	0.7 - 1.1	1.2 - 1.6	≥ 1.7
		> 2 years to 5 years	< 0.6	0.6 - 1.0	1.1 - 1.7	1.8 - 2.4	≥ 2.5
		> 5 years to 12 years	< 0.7	0.7 - 1.1	1.2 - 2.0	2.1 - 2.9	≥ 3.0
		> 12 years to 18 years	< 1.0	1.0 - 1.6	1.7 - 2.8	2.9 - 4.1	≥ 4.2

(adapted from Kawasaki T, Shime N, Straney L, et al. Paediatric sequential organ failure assessment score (pSOFA): a plea for the world-wide collaboration for consensus. *Intensive Care Med*. 2018;44(6):995-997; Schlapbach LJ, Straney L, Bellomo R, et al. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. *Intensive Care Med*. 2018;44(2):179-188; Matics TJ, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. *JAMA Pediatr.* 2017;171(10):e172352[13]; Shime N, Kawasaki T, Nakagawa S. Proposal of a New Pediatric Sequential Organ Failure Assessment Score for Possible Validation. *Pediatr Crit Care Med.* 2017;18(1):98-99)

Table e4. PELOD-2 score

PELOD-2 score								
Variable	**Age group**	**Points by severity levels**						
		0	**1**	**2**	**3**	**4**	**5**	**6**
Neurologic[1]								
GCS		≥ 11	5-10			3-4		
Pupils		Both reactive					Both fixed	
Cardiovascular[2]								
Lactatemia (mmol/L)		< 5.0	5.0 – 10.9			≥ 11.0		
Mean Arterial Pressure (MAP) (mmHg)	< 1 month	≥ 46		31 - 45	17 - 30			≤ 16
	1 – 11 months	≥ 55		39 - 54	25 - 38			≤ 24
	12 – 23 months	≥ 60		44 - 59	31 - 43			≤ 30
	24 – 59 months	≥ 62		46 - 61	32 - 44			≤ 31
	60 – 143 months	≥ 65		49 - 64	36 - 48			≤ 35
	≥ 144 months	≥ 67		52 - 66	38 - 51			≤ 37
Renal								
Creatinine *(µmol/L)*	< 1 month	≤ 69		≥ 70				
	1 – 11 months	≤ 22		≥ 23				

	12 – 23 months	≤ 34		≥ 35				
	24 – 59 months	≤ 50		≥ 51				
	60 – 143 months	≤ 58		≥ 59				
	≥ 144 months	≤ 92		≥ 93				
Respiratory[3]								
PaO_2 (mmHg)/FiO_2		≥ 61		≤ 60				
$PaCO_2$ (mmHg)		≤ 58	59 - 94		≥ 95			
Mechanical ventilation		No			Si			
Hematologic								
White cell count ($x10^3/\mu L$)		> 2		≤ 2				
Platelets ($x10^3/\mu L$)		> 142	77 - 141	≤ 76				

[1]Neurologic dysfunction: Glasgow Coma Score: use the lowest value. If the patient is sedated, record the estimated Glasgow Coma Score before sedation. Assess only patients with known or suspected acute central nervous system disease. Pupillary reactions: nonreactive pupils must be > 3 mm. Do not assess after iatrogenic pupillary dilatation.

[2]Cardiovascular dysfunction: Heart rate and mean arterial pressure: do not assess during crying or iatrogenic agitation.

[3]Respiratory dysfunction: FiO_2: fraction of inspired oxygen. PaO_2: use arterial measurement only. PaO_2/FiO_2 ratio is considered normal in children with cyanotic heart disease. $PaCO_2$ can be measured from arterial, capillary, or venous samples. Invasive ventilation: the use of mask ventilation is not considered invasive ventilation (adapted from Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med.* 2013;41(7):1761-1773)

Table e5. Pediatric MODS

System	Variable	Points by severity levels				
		0	**1**	**2**	**3**	**4**
Metabolic	**Lactates (mmol/L)**	< 1	≥ 1 and < 2	≥ 2 and < 5	≥ 5 and < 7	≥ 7.5
Respiratory	**PaO_2/FiO_2**	≥ 150	< 150 and ≥ 100	< 100 and ≥ 75	< 75 and ≥ 50	< 50
Hepatic	**Bilirubin (μmol/L)**	< 8.5	≥ 8.5 and < 34.2	≥ 34.2 and < 85.5	≥ 85.5 and < 171	≥ 171
Coagulation	**Fibrinogen (gr/L)**	≥ 1.5	< 1.5 and ≥ 1.25	< 1.25 and ≥ 1.0	< 1.0 and ≥ 0.75	< 0.75
Renal	**Blood Urea Nitrogen (BUN) (mmol/L)**	< 7.10	≥ 1 and < 2	≥ 2 and < 5	≥ 5 and < 7	≥ 7.5

(adapted from Graciano AL, Balko JA, Rahn DS, et al. The Pediatric Multiple Organ Dysfunction Score (P-MODS): Development and validation of an objective scale to measure the severity of multiple organ dysfunction in critically ill children: *Crit Care Med*. 2005;33(7):1484–91

Table e6. Pediatric qSOFA score

Variable	Age group	Points by severity levels	
		0	1
Tachypnea			
Respiratory Rate (RR) (brpm)	< 1 week	≤ 195	> 195
	> 1 week to 1 month		
	> 1 month to 2 years		
	> 2 years to 5 years		
	> 5 years to 12 years		
	> 12 years to 18 years	≤ 150	> 150
Hypotension			
Systolic Blood Pressure (SBP) (mmHg)	< 1 week	≥ 65	< 65
	> 1 week to 1 month	≥ 75	< 75
	> 1 month to 2 years	≥ 75	< 75
	> 2 years to 5 years	≥ 75	< 75
	> 5 years to 12 years	≥ 85	< 85
	> 12 years to 18 years	< 95	< 95
Altered mental status			
GCS		15	< 15

(adapted from Schlapbach LJ, Straney L, Bellomo R, et al. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. *Intensive Care Med*. 2018;44(2):179-188)

Table e7. Pediatric qSOFA-L score

Variable	Age group	Points by severity levels	
		0	1
Tachypnea			
Respiratory Rate (RR) (brpm)	< 1 week	≤ 195	> 195
	> 1 week to 1 month		
	> 1 month to 2 years		
	> 2 years to 5 years		
	> 5 years to 12 years		
	> 12 years to 18 years	≤ 150	> 150
Hypotension			
Systolic Blood Pressure (SBP) (mmHg)	< 1 week	≥ 65	< 65
	> 1 week to 1 month	≥ 75	< 75
	> 1 month to 2 years	≥ 75	< 75
	> 2 years to 5 years	≥ 75	< 75
	> 5 years to 12 years	≥ 85	< 85
	> 12 years to 18 years	< 95	< 95
Altered mental status			
GCS		15	< 15
Lactates			
Lactates (mmol/L)		≤ 2	> 2

(adapted from van Nassau SC, van Beek RH, Driessen GJ, et al. Translating Sepsis-3 Criteria in Children: Prognostic Accuracy of Age-Adjusted Quick SOFA Score in Children Visiting the Emergency Department With Suspected Bacterial Infection. *Front Pediatr*. 2018;6:266)

Table e8. Quick PELOD-2 score

Variable	Age group	Points by severity levels	
		0	1
Tachycardia			
Heart rate (HR) (bepm)	< 12 years	≤ 195	> 195
	≥ 12 years	≤ 150	> 150
Hypotension			
Systolic Blood Pressure (SBP) (mmHg)	< 1 month	≥ 65	< 65
	1 – 11 months	≥ 75	< 75
	12 – 23 months	≥ 75	< 75
	24 – 59 months	≥ 75	< 75
	60 – 143 months	≥ 85	< 85
	≥ 144 months	< 95	< 95
Altered mental status			
GCS		≥ 11	< 11

(adapted from Leclerc F, Duhamel A, Deken V, et al. Can the Pediatric Logistic Organ Dysfunction-2 Score on Day 1 Be Used in Clinical Criteria for Sepsis in Children? *Pediatr Crit Care Med* 2017;18(8):758–63)

POPC score

Table e9. POPC score

Normal	Healthy, alert and capable of normal age-appropriate activities of daily life
Mild disability	Possibility of minor physical problem that is still compatible with normal life; conscious and able to function independently
Moderate disability	Possibility of moderate disability from non-cerebral systems dysfunction alone or with cerebral dysfunction; performs independent activities of daily life but disabled for competitive performance at school
Severe disability	Possibility of severe disability from noncerebral systems dysfunction alone or with cerebral system dysfunction; conscious but dependent on others for activities of daily living support
Vegetative/coma	Vegetative state
Brain death or death	Death of the patient

(From Fiser DH. Assessing the outcome of pediatric intensive care. *J Pediatr*. 1992 Jul;121(1):68-74)

AUROC tables

Table e10. Comparison of qSOFA, SOFA (Schlapbach), SOFA (Matics PaO_2 version), SOFA (Matics SpO_2 version), SOFA (Shime version), qPELOD-2 with SIRS 3 criteria, SIRS 4 criteria, severe sepsis at discriminating mortality

Mortality: scores in comparison		**SIRS 3 criteria**		**SIRS 4 criteria**		**Severe sepsis**	
Scoring system	**AUC (95% CI)**	**AUC (95% CI)**	***P* value for AUC comparison**	**AUC (95% CI)**	***P* value for AUC comparison**	**AUC (95% CI)**	***P* value for AUC comparison**
qSOFA	0.866 (0.808-0.925)	0.509 (0.218-0.799)	0.021	0.616 (0.560-0.672)	< 0.001	0.527 (0.497-0.557)	< 0.001
qSOFA-L	0.880 (0.754-1.000)	"	0.024	"	< 0.001	"	< 0.001
SOFA (*Schlapbach)*	0.929 (0.812-1.000)	"	0.010	"	< 0.001	"	< 0.001
SOFA (*Matics PaO_2 version*)	0.855 (0.657-1.000)	"	0.057	"	< 0.001	"	0.002
SOFA (*Matics SpO_2 version*)	0.830 (0.588-1.000)	"	0.099	"	0.026	"	0.018
SOFA (*Shime version*)	0.882 (0.727-1.000)	"	0.029	"	0.096	"	< 0.001
qPELOD-2	0.830 (0.763-0.898)	"	0.008	"	0.002	"	< 0.001
P-MODS	0.862 (0.654-1.000)	"	0.056	"	0.029	"	0.003
AUC: Area under the ROC Curve							

Table e11. Comparison of qSOFA, SOFA (Schlapbach), SOFA (Matics PaO_2 version), SOFA (Matics SpO_2 version), SOFA (Shime version), qPELOD-2 with SIRS 3 criteria, SIRS 4 criteria, severe sepsis at discriminating a poor "outcome" (ΔPOPC ≥ 1 or death)

New disability (ΔPOPC ≥ 1) or death: scores in comparison		**SIRS 3 criteria**		**SIRS 4 criteria**		**Severe sepsis**	
Scoring system	**AUC (95% CI)**	**AUC (95% CI)**	***P* value for AUC comparison**	**AUC (95% CI)**	***P* value for AUC comparison**	**AUC (95% CI)**	***P* value for AUC comparison**
qSOFA	0.733 (0.595-0.870)	0.594 (0.429-0.759)	0.197	0.633 (0.570-0.695)	0.197	0.525 (0.432-0.618)	0.016
qSOFA-L	0.724 (0.557-0.890)	"	0.280	"	0.320	"	0.044
SOFA (*Schlapbach)*	0.710 (0.512-0.910)	"	0.379	"	0.468	"	0.101
SOFA (*Matics PaO_2 version*)	0.707 (0.533-0.881)	"	0.356	"	0.434	"	0.074
SOFA (*Matics SpO_2 version*)	0.704 (0.531-0.877)	"	0.366	"	0.448	"	0.077
SOFA (*Shime version*)	0.742 (0.564-0.920)	"	0.233	"	0.260	"	0.037
qPELOD-2	0.748 (0.611-0.885)	"	0.138	"	0.138	"	0.010
P-MODS	0.653 (0.418-0.888)	"	0.690	"	0.870	"	0.324
AUC: Area under the ROC Curve							

Table e12. Comparison of qSOFA, SOFA (Schlapbach), SOFA (Matics PaO_2 version), SOFA (Matics SpO_2 version), SOFA (Shime version), qPELOD-2 with SIRS 3 criteria, SIRS 4 criteria, severe sepsis at discriminating PICU LOS > 5 days

PICU LOS > 5 days: scores in comparison		**SIRS 3 criteria**		**SIRS 4 criteria**		**Severe sepsis**	
Scoring system	**AUC (95% CI)**	**AUC (95% CI)**	***P* value for AUC comparison**	**Scoring system**	**AUC (95% CI)**	**AUC (95% CI)**	***P* value for AUC comparison**
qSOFA	0.656 (0.531-0.779)	0.5192 (0.390-0.649)	0.139	0.5215 (0.416-0.627)	0.110	0.544 (0.496-0.593)	0.105
qSOFA-L	0.626 (0.493-0.759)	"	0.353	"	0.203	"	0.253
SOFA (*Schlapbach)*	0.622 (0.480-0.765)	"	0.297	"	0.269	"	0.313
SOFA (*Matics PaO_2 version*)	0.589 (0.442-0.735)	"	0.487	"	0.467	"	0.572
SOFA (*Matics SpO_2 version*)	0.604 (0.459-0.750)	"	0.395	"	0.370	"	0.446
SOFA (*Shime version*)	0.609 (0.465-0.753)	"	0.365	"	0.338	"	0.404
qPELOD-2	0.611 (0.483-0.740)	"	0.577	"	0.558	"	0.699
P-MODS	0.565 (0.415-0.715)	"	0.783	"	0.589	"	0.782

AUC: Area under the ROC Curve
PICU: Pediatric Intensive Care Unit
LOS: Length of Stay

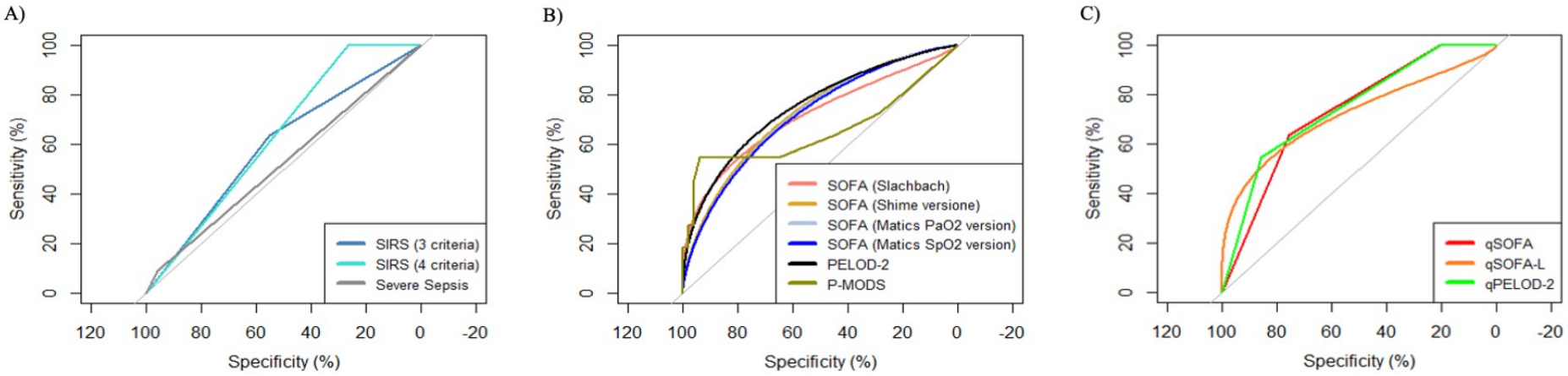
***Table e13*.** Comparison of qSOFA, SOFA (Schlapbach), SOFA (Matics PaO_2 version), SOFA (Matics SpO_2 version), SOFA (Shime version), qPELOD-2 with SIRS 3 criteria, SIRS 4 criteria, severe sepsis at discriminating duration of invasive MV > 3 days

Duration of invasive MV > 3 days: scores in comparison		**SIRS 3 criteria**		**SIRS 4 criteria**		**Severe sepsis**	
Scoring system	**AUC (95% CI)**	**AUC (95% CI)**	***P* value for AUC comparison**	**Scoring system**	**AUC (95% CI)**	**AUC (95% CI)**	***P* value for AUC comparison**
qSOFA	0.634 (0.505-0.764)	0.506 (0.370-0.641)	0.180	0.517 (0.403-0.630)	0.182	0.539 (0.496-0.581)	0.172
qSOFA-L	0.630 (0.491-0.769)	"	0.211	"	0.217	"	0.221
SOFA (*Schlapbach)*	0.610 (0.468-0.751)	"	0.298	"	0.314	"	0.346
SOFA (*Matics P_aO2 version*)	0.590 (0.446-0.734)	"	0.405	"	0.435	"	0.506
SOFA (*Matics SpO2 version*)	0.593 (0.450-0.736)	"	0.387	"	0.414	"	0.478
SOFA (*Shime version*)	0.597 (0.453-0.740)	"	0.368	"	0.393	"	0.451
qPELOD-2	0.632 (0.506-0.758)	"	0.239	"	0.246	"	0.247
P-MODS	0.597 (0.446-0.748)	"	0.378	"	0.405	"	0.467

AUC: Area under the ROC Curve
MV: Mechanical ventilation

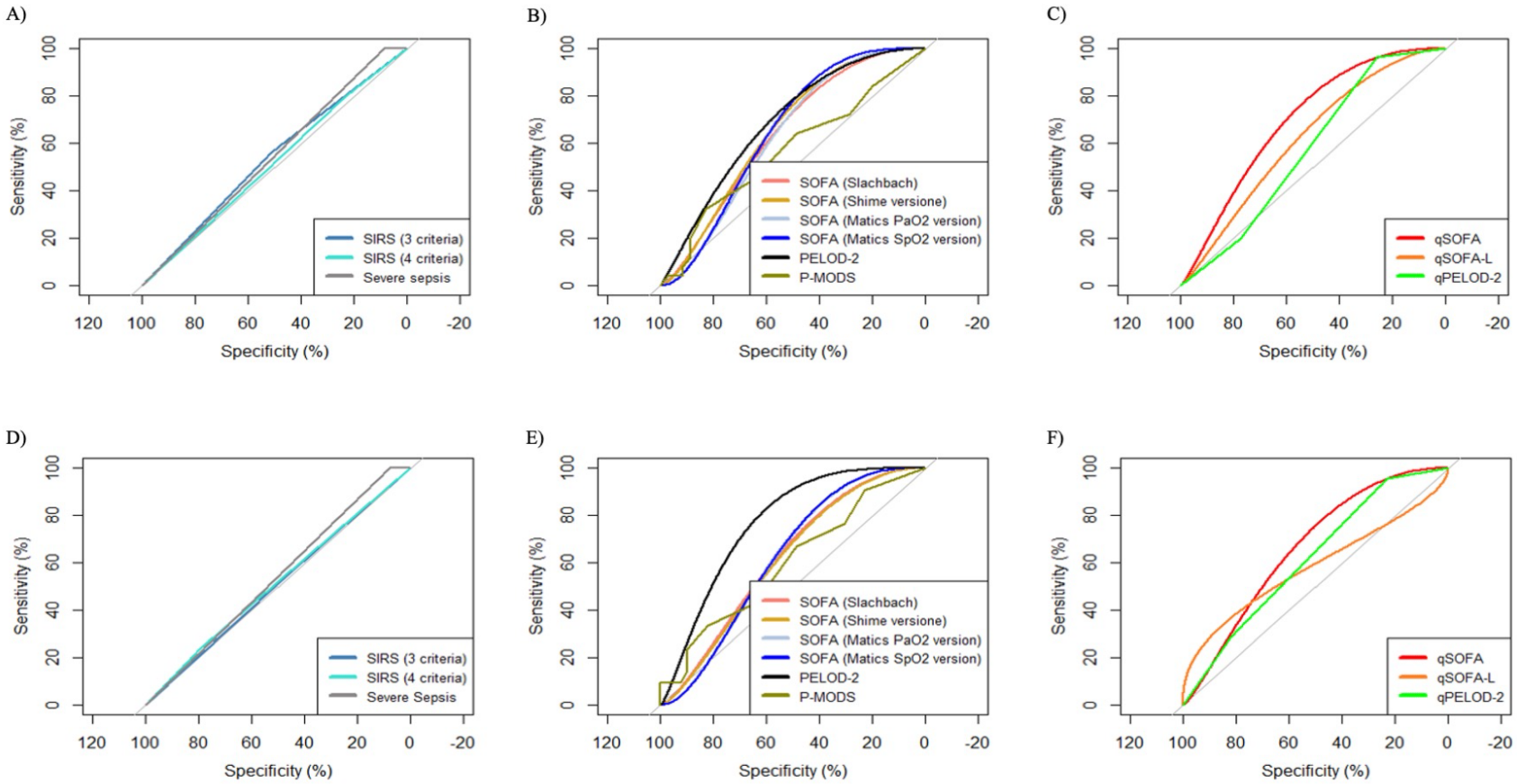
AUROC curves

Figure e2. Comparison of AUROC curves at discriminating a "poor outcome" (ΔPOPC ≥ 1 or death)



In particular: A) Comparison between SIRS 3 criteria, SIRS 4 criteria, severe sepsis for ΔPOPC ≥ 1 or death; B) Comparison between SOFA (Schlapbach version), SOFA (Shime version), SOFA (Matics PaO_2 version), SOFA (Matics SpO_2 version), PELOD-2, P-MODS for ΔPOPC ≥ 1 or death; C) Comparison between qSOFA, qSOFA-L, qPELOD-2 for ΔPOPC ≥ 1 or death.

Figure e3. Comparison of AUROC curves at discriminating PICU LOS > 5 days and duration of invasive MV > 3 days



In particular: A) Comparison between SIRS 3 criteria, SIRS 4 criteria, severe sepsis for PICU LOS > 5 days; B) Comparison between SOFA (Schlapbach version), SOFA (Shime version), SOFA (Matics PaO_2 version), SOFA (Matics SpO_2 version), PELOD-2, P-MODS for PICU LOS > 5 days; C) Comparison between qSOFA, qSOFA-L, qPELOD-2 for PICU LOS > 5 days; D) Comparison between SIRS 3 criteria, SIRS 4 criteria, severe sepsis for duration of invasive MV > 3 days; E) Comparison between SOFA (Schlapbach version), SOFA (Shime version), SOFA (Matics PaO_2 version), SOFA (Matics SpO_2 version), PELOD-2, P-MODS for duration of invasive MV > 3 days; E) Comparison between qSOFA, qSOFA-L, qPELOD-2 for duration of invasive MV > 3 days.

Characteristics	**Overall**	**Group 1 (SIRS criteria met at 24h)**	**Group 2 (SIRS criteria not met at 24h)**	***p* value**
	N = 466	N = 261 (56,01%)	N = 205 (43,99%)	
Infection site				
CNS, no (%)	46 (9,87%)	24 (9,20%)	22 (10,73%)	0,581
Lower respiratory tract, no (%)	258 (55,36%)	128 (49,04%)	130 (63,41%)	0,002
Higher respiratory tract, no (%)	30 (6,44%)	18 (6,90%)	12 (5,85%)	0,649
Heart, no (%)	2 (0,43%)	2 (0,77%)	0 (0%)	0,209
Gastrointestinal tract, no (%)	35 (7,51%)	25 (9,58%)	10 (4,88%)	0,056
Genitourinary tract, no (%)	9 (1,93%)	6 (2,30%)	3 (1,46%)	0,515
Bloodstream, no (%)	22 (4,72%)	20 (7,66%)	2 (0,98%)	0,001
Other, no (%)	16 (3,43%)	8 (3,07%)	8 (3,90%)	0,622
Unidentified, no (%)	48 (10,30%)	30 (11,49%)	18 (8,78%)	0,339
Infection source				
Community-acquired, no (%)	403 (86,48%)	218 (83,52%)	185 (90,24%)	0,035
Hospital-acquired, no (%)	63 (13,52%)	43 (16,48%)	20 (9,76%)	
Infection diagnosis				
Suspected, no (%)	184 (39,57%)	105 (40,23%)	79 (38,73%)	0,742
Confirmed, no (%)	281 (60,43%)	156 (59,77%)	125 (61,27%)	
Isolated microorganism				
Bacteria, all, no (%)	122 (26,18%)	91 (34,87%)	31 (15,12%)	< 0,001
S. aureus, no (%)	12 (2,58%)	7 (2,68%)	5 (2,44%)	0,869
S. pyogenes, no (%)	10 (2,15%)	9 (3,45%)	1 (0,49%)	0,029
S. pneumoniae, no (%)	22 (4,72%)	16 (6,13%)	6 (2,93%)	0,106
Gram+, other, no (%)	15 (3,22%)	9 (3,45%)	6 (2,93%)	0,752
E. coli, no (%)	12 (2,58%)	10 (3,83%)	2 (0,98%)	0,053
K. pneumoniae, no (%)	15 (3,22%)	11 (4,21%)	4 (1,95%)	0,169
P. aeruginosa, no (%)	13 (2,79%)	11 (4,21%)	2 (0,98%)	0,035
Gram-, other, no (%)	28 (6,01%)	22 (8,43%)	6 (2,93%)	0,013
Virus, all, no (%)	189 (40,56%)	80 (30,65%)	109 (53,17%)	< 0,001
HSV, no (%)	2 (0,43%)	1 (0,38%)	1 (0,49%)	0,864

CMV, no (%)	3 (0,64%)	2 (0,77%)	1 (0,49%)	0,709
Influenza, no (%)	20 (4,29%)	10 (3,83%)	10 (4,88%)	0,58
SARS-CoV-2, no (%)	16 (3,43%)	8 (3,07%)	8 (3,90%)	0,622
Virus, other, no (%)	155 (33,26%)	62 (23,75%)	93 (45,37%)	< 0,001
Fungi, all, no (%)	6 (1,29%)	5 (1,92%)	1 (0,49%)	0,175
Candida spp, no (%)	4 (0,86%)	3 (1,15%)	1 (0,49%)	0,442
Aspergillus spp, no (%)	1 (0,21%)	1 (0,38%)	0 (0%)	0,375
Parasites, no (%)	1 (0,21%)	1 (0,38%)	0 (0%)	0,375
Unidentified, no (%)	185 (39,70%)	105 (40,23 %)	80 (30,92%)	0,792
Antibiotic therapy, no (%)	437 (93,78%)	256 (98,08%)	181 (88,29%)	< 0,001
Beta-lactams, no (%)	411 (88,20%)	241 (92,34%)	170 (82,93%)	0,002
Penicillins, no (%)	187 (40,13%)	100 (38,31%)	87 (42,44%)	0,367
Cephalosporins, no (%)	195 (41,85%)	113 (43,30%)	82 (40,00%)	0,474
Carbapenems, no (%)	56 (12,02%)	47 (18,01%)	9 (4,39%)	< 0,001
Glycopeptides, no (%)	87 (18,67%)	67 (25,67%)	20 (9,76%)	< 0,001
Aminoglycosides, no (%)	40 (8,58%)	26 (9,96%)	14 (6,83%)	0,231
Macrolides, no (%)	90 (19,31%)	57 (21,84%)	33 (16,10%)	0,119
Linezolid, no (%)	21 (4,51%)	16 (6,13%)	5 (2,44%)	0,057
Antiviral therapy, no (%)	74 (15,88%)	37 (14,18%)	37 (18,05%)	0,256
Antimycotic therapy, no (%)	59 (12,66%)	44 (16,86%)	15 (7,32%)	0,002

Table e14. Infection, microbiology and antimicrobial therapy in enrolled patients.

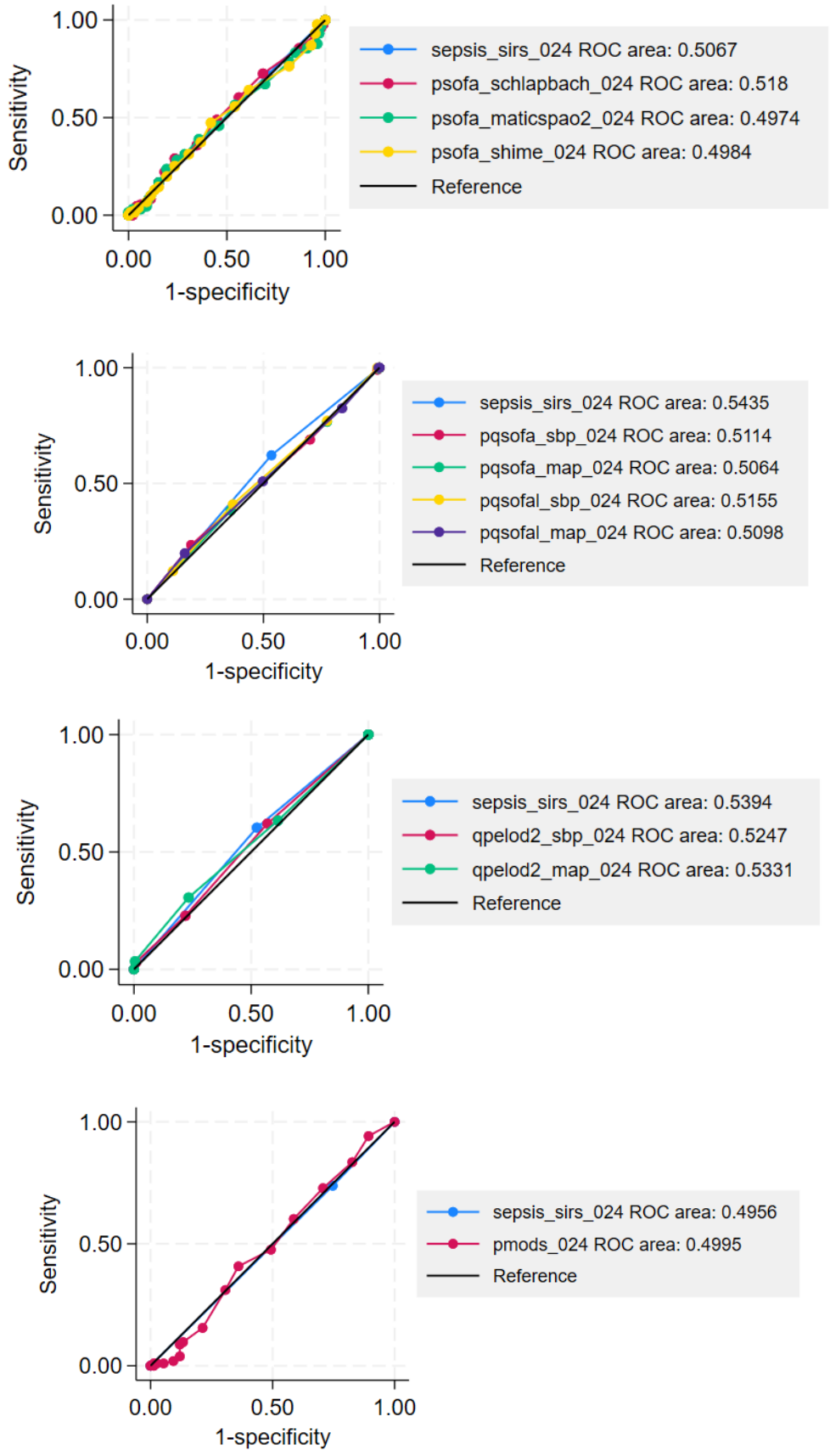


Figure e4. Predictive performance for duration of mechanical ventilation > 5 days for all prognostic scores measured at the Day 1 time-interval, compared to SIRS criteria.

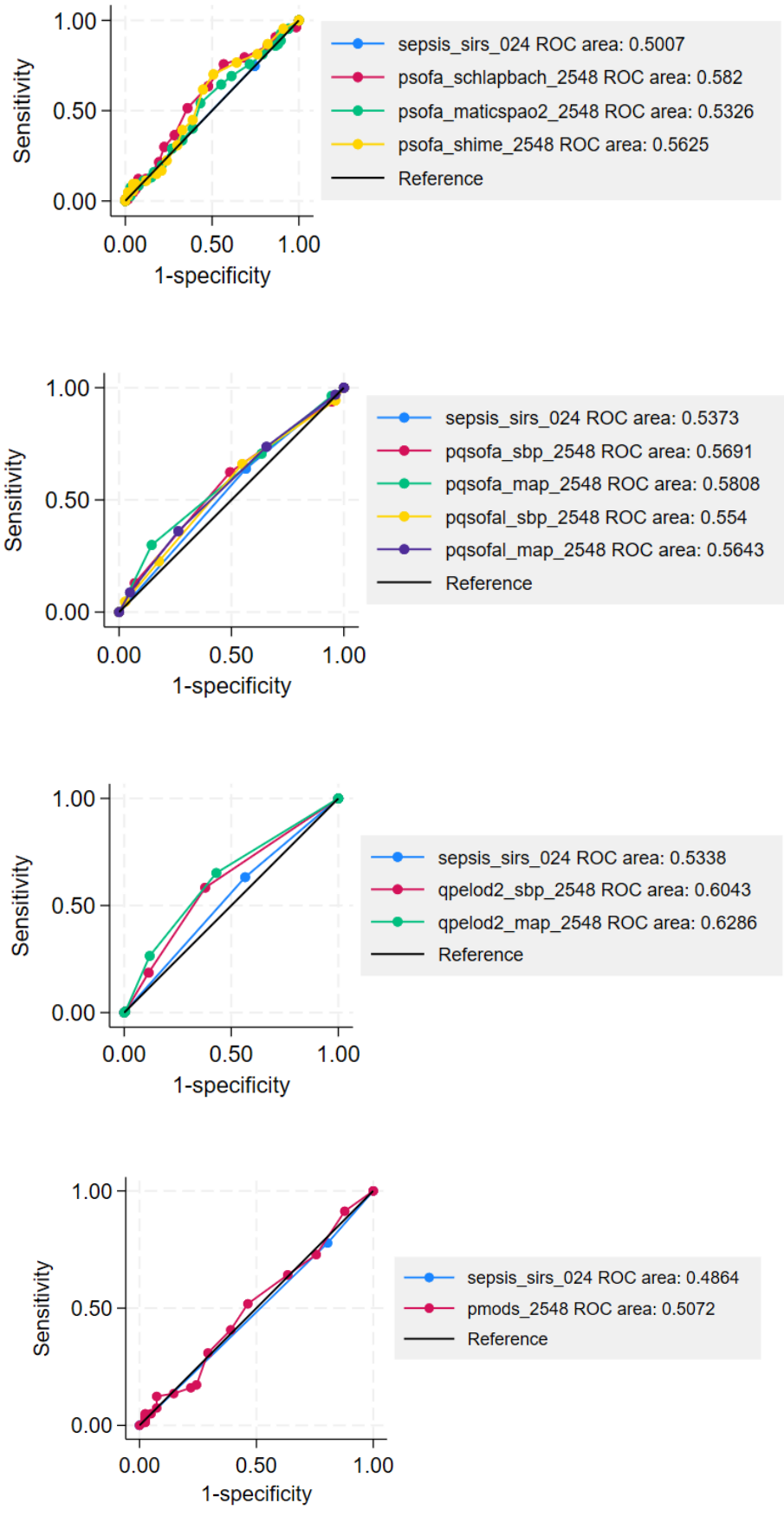


Figure e5. Predictive performance for duration of mechanical ventilation > 5 days for all prognostic scores measured at the Day 2 time-interval, compared to SIRS criteria.

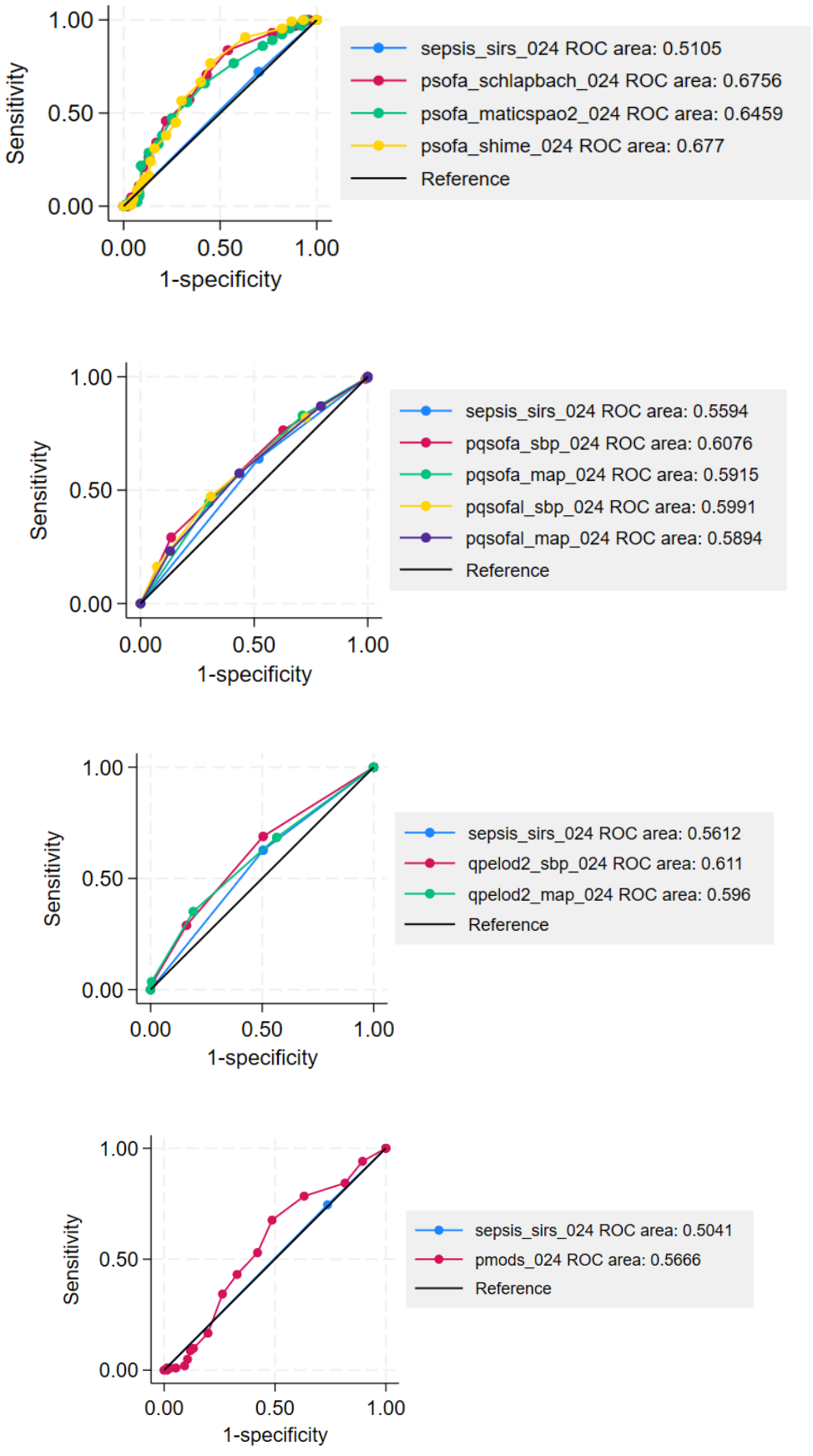


Figure e6. Predictive performance for duration of PICU length of stay> 5 days for all prognostic scores measured at the Day 1 time-interval, compared to SIRS criteria.

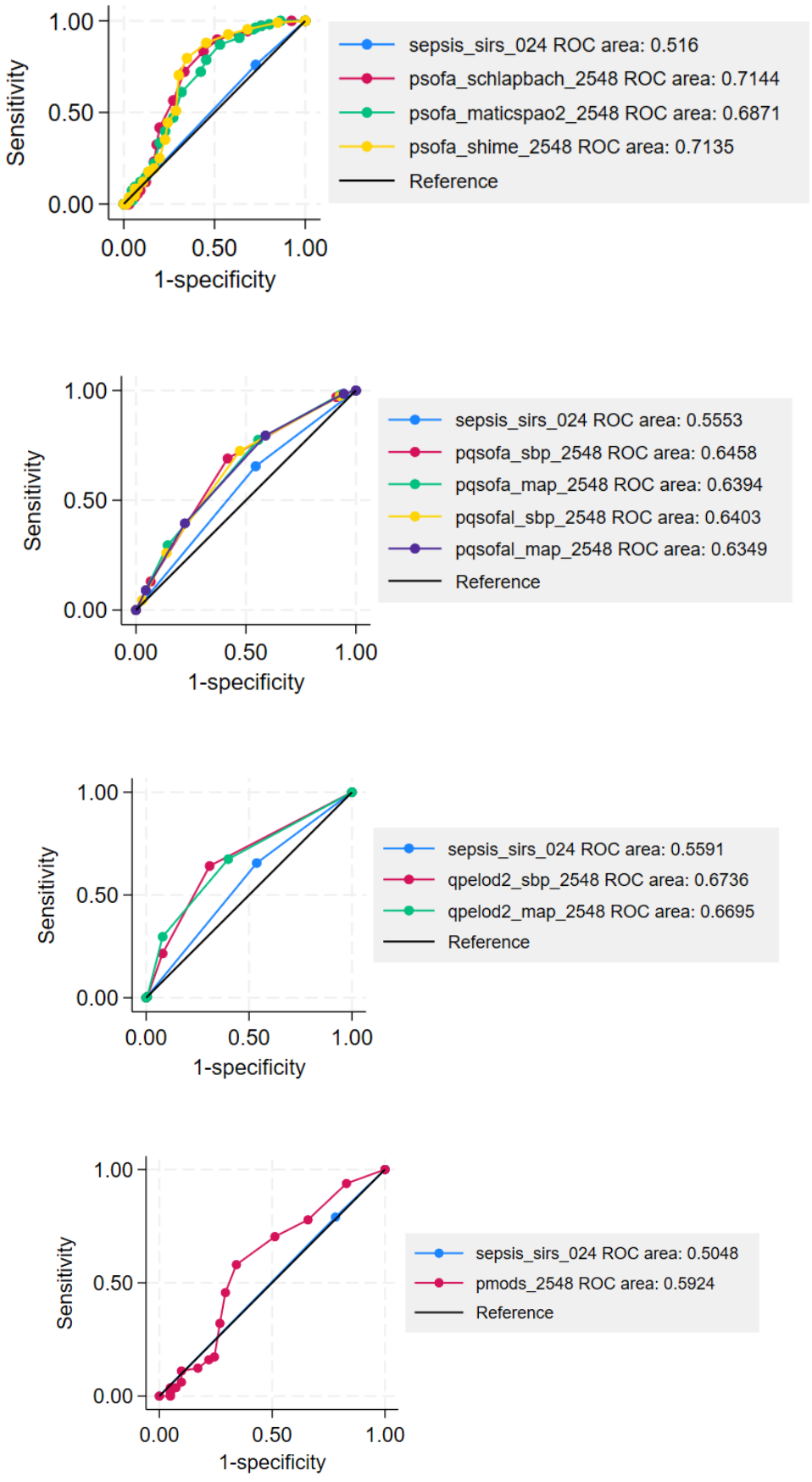
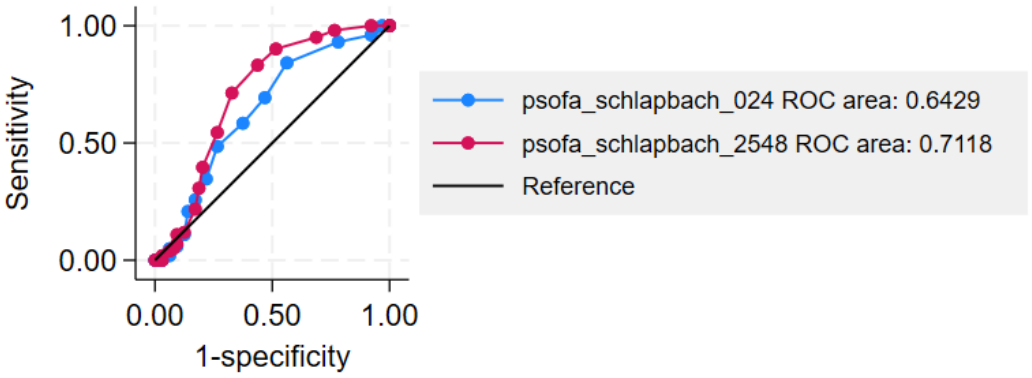
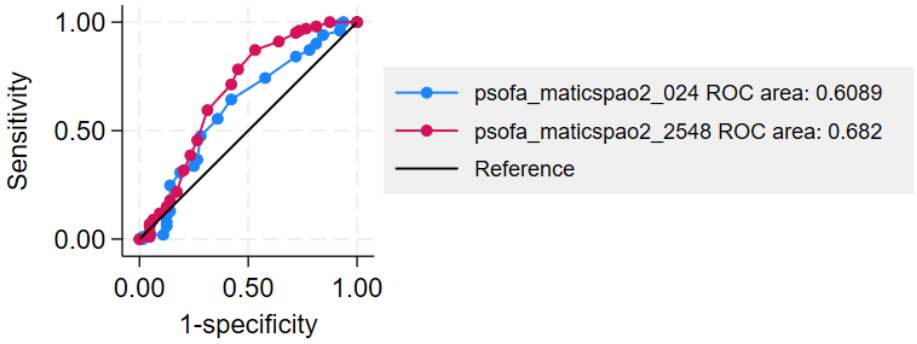
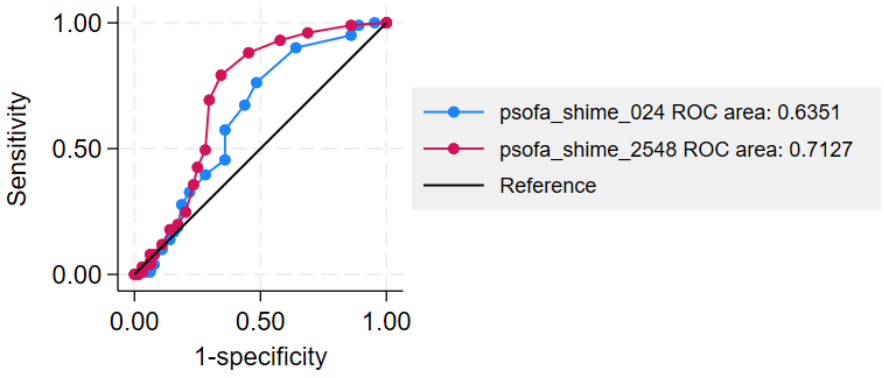
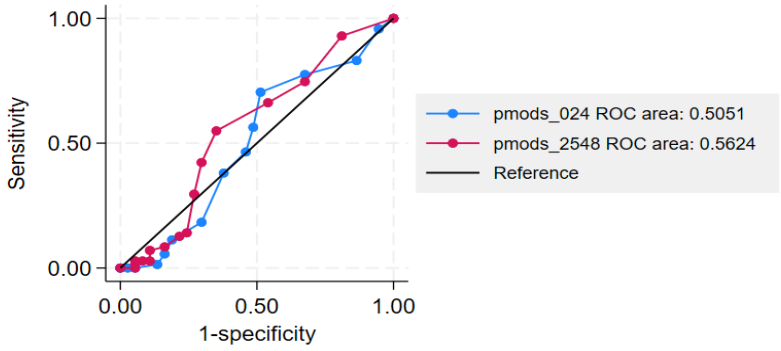


Figure e7. Predictive performance for duration of PICU length of stay> 5 days for all prognostic scores measured at the Day 2 time-interval, compared to SIRS criteria.


Sensitivity
1.00
0.50
0.00
0.00
0.50
1.00
1-specificity
psofa_schlapbach_024 ROC area: 0.6429
psofa_schlapbach_2548 ROC area: 0.7118
Reference


Sensitivity
1.00
0.50
0.00
0.00
0.50
1.00
1-specificity
psofa_maticspao2_024 ROC area: 0.6089
psofa_maticspao2_2548 ROC area: 0.682
Reference


Sensitivity
1.00
0.50
0.00
0.00
0.50
1.00
1-specificity
psofa_shime_024 ROC area: 0.6351
psofa_shime_2548 ROC area: 0.7127
Reference


Sensitivity
1.00
0.50
0.00
0.00
0.50
1.00
1-specificity
pmods_024 ROC area: 0.5051
pmods_2548 ROC area: 0.5624
Reference

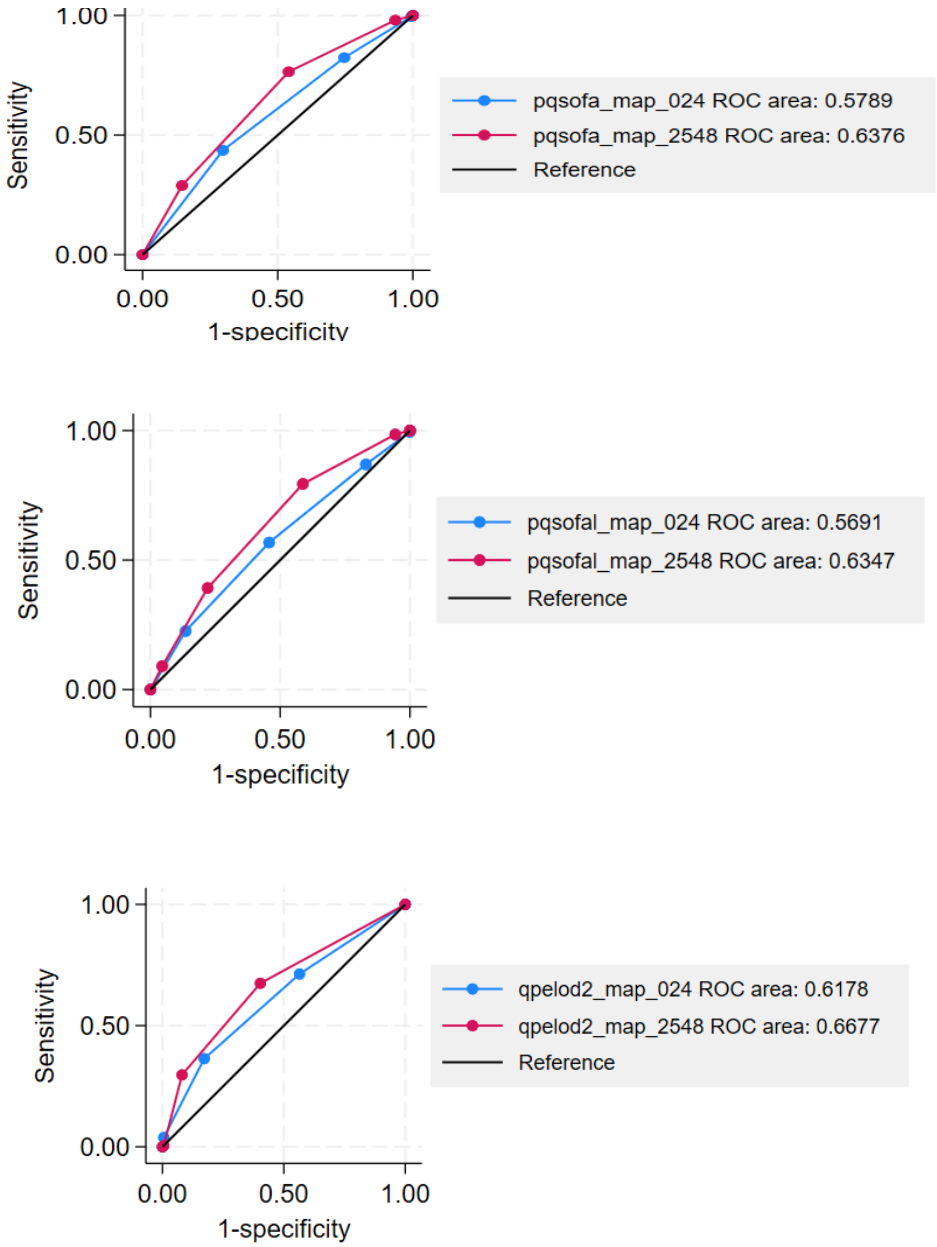


Figure e8. Comparison of performance of prognostic scores measured separately at Day 1 and Day 2 for duration of PICU length of stay > 5 days.

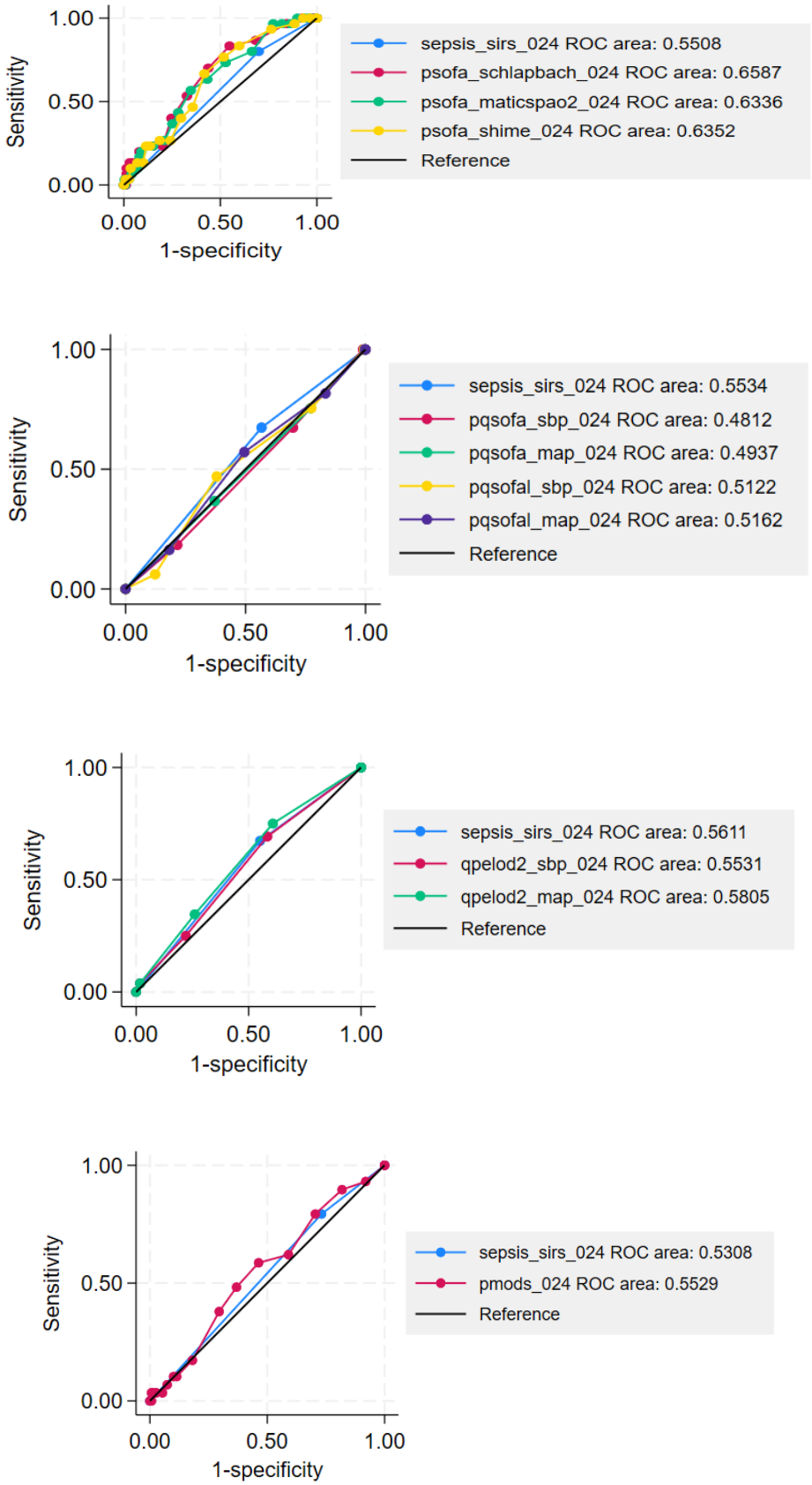


Figure e9. Predictive performance for POPC score difference for all prognostic scores measured at the Day 1 time-interval, compared to SIRS criteria.

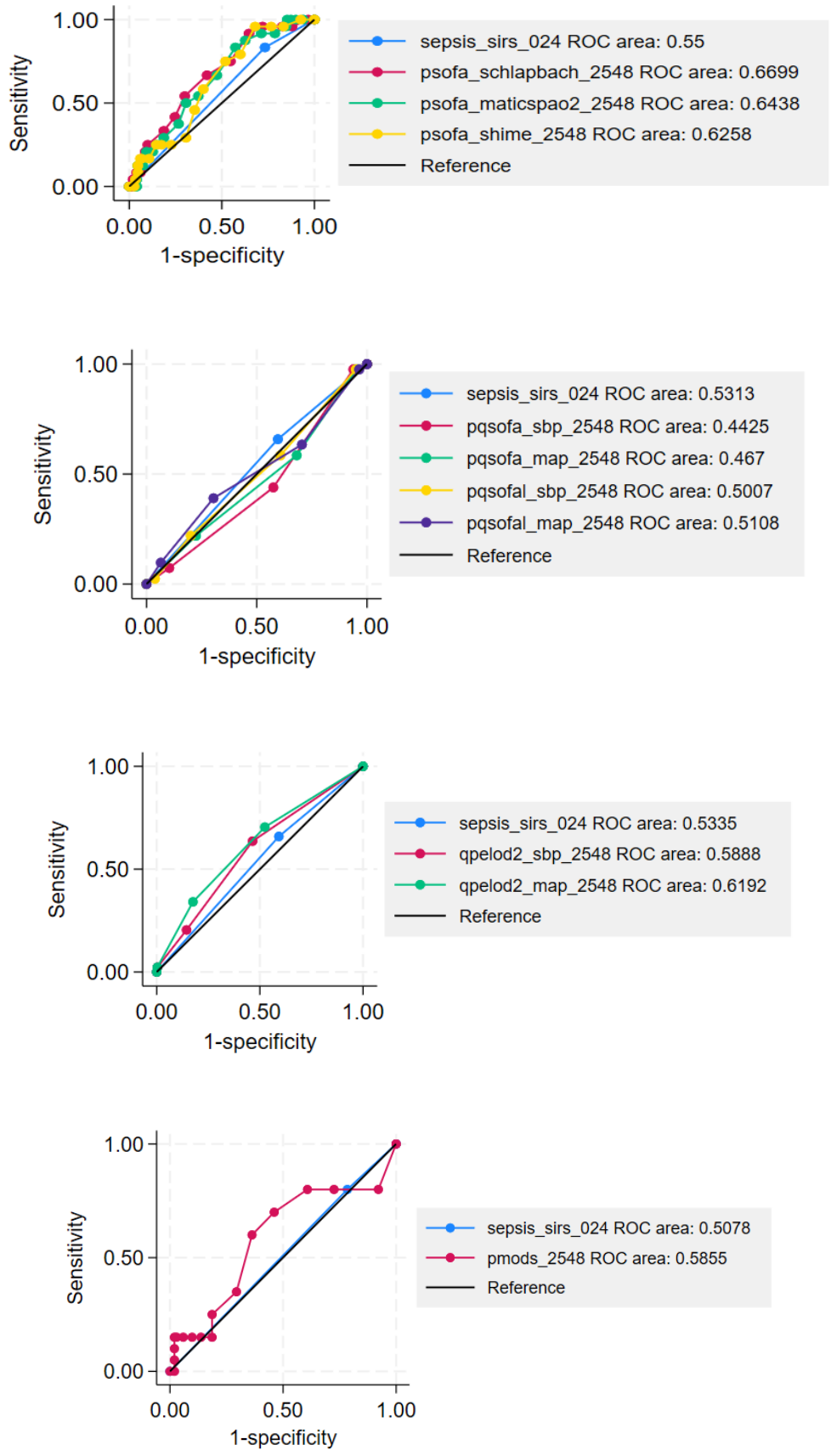


Figure e10. Predictive performance for POPC score difference for all prognostic scores measured at the Day 2 time-interval, compared to SIRS criteria.

Abstract 469

COMPARISON OF THE PHOENIX SEPSIS SCORE WITH OTHER PROGNOSTIC SCORES IN A COHORT OF CHILDREN WITH INFECTION ADMITTED TO THE PICU: A MULTI-CENTER ITALIAN STUDY

Type: Abstract Submission

Topic: AS08. Infection, systemic inflammation and sepsis

Authors: Luca Marchetto, Rosanna Irene Comoretto, Fabrizio Zoppelletto, Davide Padrin, Paolo Biban, Stefania Ferrario, Maria Cristina Mondardini, Giulia Bordin, Pasquale Vitale, Enzo Picconi, Immacolata Rulli, Andrea Wolfler, Dario Gregori, Angela Amigoni, Marco Daverio; Italy

Background and Amis

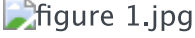
The new Phoenix Sepsis Score has been recently introduced to diagnose and prognosticate pediatric sepsis and replace the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) definitions. We aimed to compare the Phoenix Sepsis Score prognostic performance with other organ-dysfunction scores in patients admitted with infection to the Pediatric Intensive Care Unit (PICU).

Methods

Multi-center prospective cohort study on pediatric patients admitted with infection to nine Italian PICUs between February 2022 and January 2024. We collected data from the first 24 hours of admission regarding the worst vital signs, markers of organ dysfunction, organ support. We calculated the following scores: pSOFA (Matics' P_aO_2/SpO_2 versions), PELOD-2, P-MODS, IPSCC Severe Sepsis, Phoenix Sepsis Score. We compared each other using the area under the ROC curve (AUROC). Primary outcome: PICU mortality. Secondary outcomes: "new disability" (POPC difference from baseline ≥1); prolonged invasive mechanical ventilation (>5 days).

Results

Among 581 patients, 22 died (3.8%), 65 (11.2%) developed new disability, 143 (24.6%) experienced prolonged invasive MV. Among the scores, Phoenix Sepsis Score showed the best performance (AUROC 0.906, CI 0.835-0.977) in predicting mortality, followed by Matics' SpO_2 pSOFA (AUROC 0.888, CI 0.814-0.963), Matics' PaO_2 pSOFA (AUROC 0.887, CI 0.820-0.954), PELOD-2 (AUROC 0.881, CI 0.794-0.967), IPSCC Severe Sepsis (AUROC 0.876, CI 0.795-0.956), and P-MODS (AUROC 0.756, CI 0.627-0.885) (Figure 1A), without statistical differences. All the scores showed low accuracy in predicting secondary outcomes (Figure 1B-C).

figure 1.jpg

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Conclusions

New Phoenix Sepsis Score confirmed high performance in predicting mortality in PICU patients with infection. Larger studies will be required for further validation.

Print

Abstract 945

INDIVIDUAL ORGAN DYSFUNCTIONS IN CHILDREN ADMITTED TO THE PICU WITH INFECTION: A MULTI-CENTER ITALIAN STUDY

Type: Abstract Submission

Topic: AS08. Infection, systemic inflammation and sepsis

Authors: Davide Padrin, Rosanna Irene Comoretto, Serena Scaravetti, Laura Di Michele, Anna Tessari, Francesco Sacco, Stefania Ferrario, Giorgia Eusebi, Giulia Bordin, Pasquale Vitale, Enzo Picconi, Immacolata Rulli, Andrea Wolfler, Dario Gregori, Marco Daverio, Luca Marchetto; Italy

Background and Amis

The new Phoenix Sepsis Score, published in January 2024, defines sepsis incorporating the concept of organ dysfunction (e.g., sepsis defined for Phoenix≥2). We aimed to describe the incidence of individual types of organ dysfunction in a large cohort of patients admitted with infection to the Pediatric Intensive Care Unit (PICU).

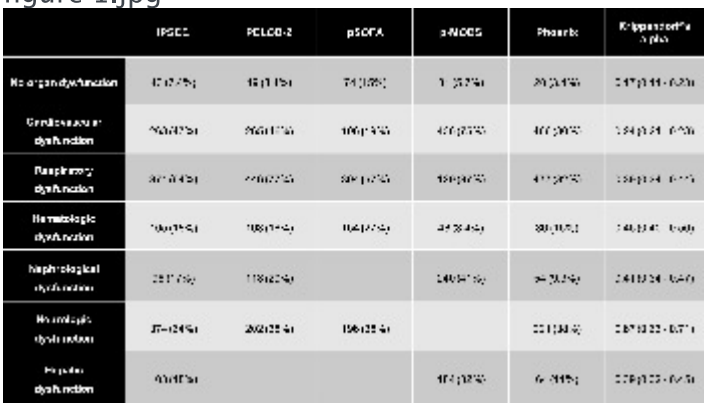
Methods

Secondary analysis of a multi-center prospective cohort study on pediatric patients admitted with infection to nine Italian PICUs between February 2022 to January 2024. We collected the “worst” variables from the first 24 hours of admission required to define individual organ dysfunctions according to the following scores: IPSCC (International Pediatric Sepsis Consensus Conference) Severe Sepsis, PELOD-2, pSOFA, P-MODS, Phoenix Sepsis Score. We assessed the agreement between the scores calculating the Krippendorff’s alpha (>0.67, acceptable).

Results

Among 581 infections, those meeting criteria for organ dysfunction by score were (Figure 1): IPSCC Severe Sepsis in 538 of 581 infection (92.6%); PELOD-2 in 532 of 581 (91.6%); pSOFA in 507 of 581 (87.3%), P-MODS in 550 of 581 infection (94.7%), Phoenix in 561 of 581 (96.6%). The most frequent individual organ dysfunction was, by score: neurologic and respiratory in IPSCC Severe Sepsis (64%), respiratory in PELOD-2, pSOFA and Phoenix (77%, 67% and 82%, respectively), cardiovascular in P-MODS (75%). The level of agreement between the scores was acceptable only for neurological dysfunction.

figure 1.jpg



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Conclusions

Organ dysfunction was common in PICU patients admitted with infection. Further analysis will be performed to determine the impact of individual organ dysfunction in contributing to clinically significant outcomes (e.g., mortality).

Print

Abstract 866

AKI AND RAI SCORE ASSOCIATION WITH CLINICALLY SIGNIFICANT OUTCOMES IN CHILDREN ADMITTED WITH INFECTION TO THE PICU: A MULTICENTER COHORT STUDY

Type: Abstract Submission

Topic: AS05. Critical Care Nephrology & Hepatology

Authors: Marco Daverio, Rosanna Irene Comoretto, Alessandra Alfisi, Giovanni Ceschia, Davide Padrin, Anna Tessari, Francesco Sacco, Stefania Ferrario, Fabio Caramelli, Giulia Bordin, Alessandra Conio, Enzo Picconi, Immacolata Rulli, Andrea Wolfler, Dario Gregori, Enrico Vidal, Angela Amigoni, Luca Marchetto; Italy

Background and Amis

Critically-ill children admitted to the Pediatric Intensive Care Unit (PICU) are at high-risk of acute kidney injury (AKI) which is associated with an increased burden of disease. The Renal Angina Index (RAI) score has been developed to predict the risk of severe AKI (i.e. stage-2 and 3). We explored the association of AKI and RAI score with clinically significant outcomes in children admitted with infection to PICU.

Methods

Secondary analysis of a prospective multi-center cohort study on pediatric patients with infection admitted to 9 Italian PICUs from February 2022 to January 2024. We investigated the association between AKI in the first 24 hours with mortality and need for Continuous Renal Replacement Therapy (CRRT). We also evaluated the relationship between a positive RAI score (i.e., >8) in the first 24 hours and the occurrence of severe AKI, need for CRRT and mortality.

Results

We enrolled 581 patients (median age 713 days), 22 (3.8%) died. Eighty-six (14.8%) patients presented with AKI, 27 (4.6%) stage-1, 18 (3.1%) stage-2 and 41 (7.1%) stage-3. Each grade of AKI demonstrated an increased odds ratio (OR) for mortality of 2.74 (interquartile range [IQR] 1.98-3.83) and need for CRRT (OR 7.73, IQR 4.02-4.29). A positive RAI score (50 [8.6%] patients) was associated with increased risk for severe AKI (OR 12.23, IQR 6.29-23.82), need for CRRT (OR 10.64, IQR 3.58-31.05) and mortality (OR 13.80, IQR 5.55-34.48).

Conclusions

Patients with infection presenting with AKI or a RAI score>8 in the first day of PICU admission demonstrate a higher risk of clinically significant outcomes.

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