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Children's Hospital Association
2024 Sepsis Webcast Series

International Consensus Criteria for Pediatric Sepsis and Septic Shock

Fran Balamuth, MD, PhD, MSCE
Christopher Horvat, MD, MHA
Halden Scott, MD, MSCS

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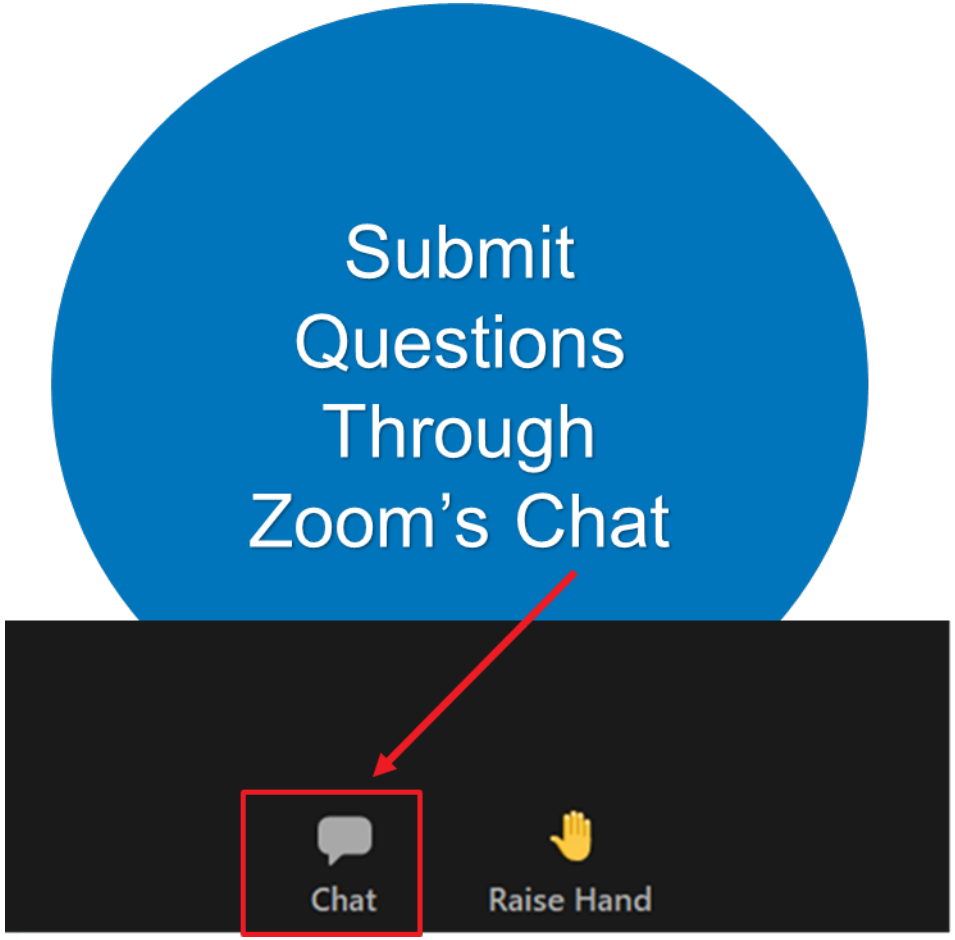
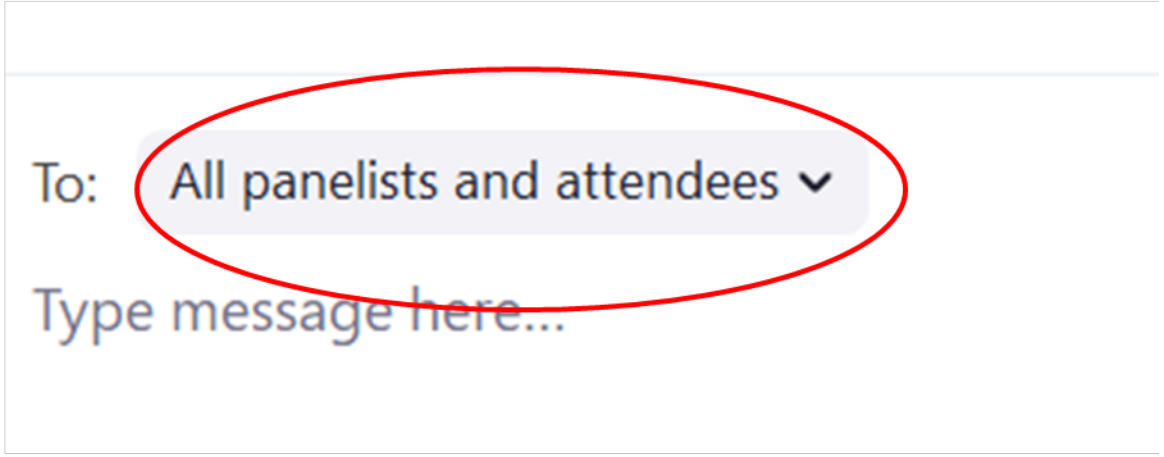


Ask: Everyone



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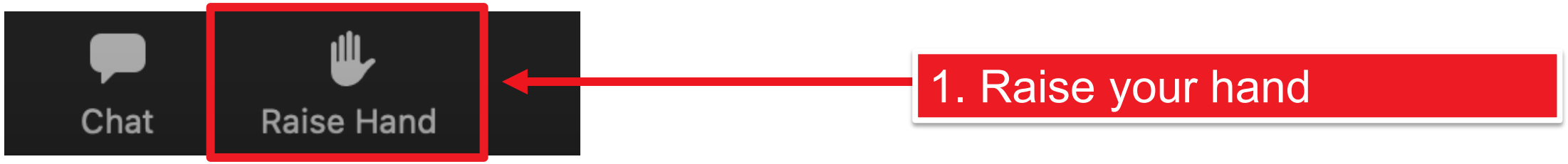

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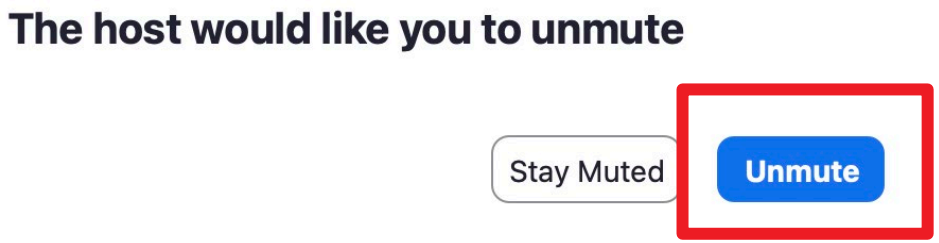
1. Raise your hand



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Questions/Comments During Discussion

You may raise your hand to share during the discussion

1. Raise your hand

3. Lower your hand

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Our Speakers

Fran Balamuth, MD, PhD, MSCE

Associate Professor of Pediatrics

University of Pennsylvania

Christopher Horvat, MD, MHA

Associate Professor of Critical Care Medicine

University of Pittsburgh Medical Center

Halden Scott, MD, MSCS

Associate Professor

University of Colorado

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Challenge sepsis.
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International Consensus Criteria for Pediatric Sepsis and Septic Shock

Fran Balamuth, MD, PhD, MSCE
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March 19, 2024

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Learning Objectives

- Explain the Phoenix criteria for pediatric sepsis and septic shock and identify opportunities to incorporate these criteria into pediatric sepsis work.

- Evaluate the differences between the Phoenix criteria and sepsis screening.

- Discuss the implications of Phoenix criteria for existing pediatric sepsis literature and current care recommendations provided by IPSO and other organizations.

Sepsis Definitions: Historical Context

Infection

Suspected or proven infection caused by any pathogen OR a clinical syndrome w/ probability of infection

Sepsis

SIRS in the presence of infection

Severe Sepsis

Sepsis + CV dysfunction OR ARDS OR ≥2 other organ dysfunction

Septic Shock

Sepsis and CV organ dysfunction (hypotension, pressors or elevated lactate)

Systemic Inflammatory Response Syndrome

(2/4, 1 must be temp or wbc):

- Core Temp > 38.5°C or <36°C
- Tachycardia / Bradycardia
- Tachypnea
- WBC elevated or depressed

(Goldstein et al., 2005)

Sepsis 3

Life-threatening organ dysfunction caused by a dysregulated host response to infection

Seymour *JAMA* 2016

VIEWPOINT

Defining Pediatric Sepsis

Luregn J. Schlapbach, MD, FCICM
Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia; and Paediatric Critical Care Research Group, Mater Research Institute, University of Queensland, Brisbane, Queensland, Australia.

Niranjan Kissoon, MD
University of British Columbia, Vancouver, British Columbia, Canada; and British

The resolution on sepsis by the United Nations World Health Assembly in May 2017 recognizes sepsis as a global threat in adults and children and a priority for the World Health Organization to address during the next decade.[1] This resolution on sepsis acknowledges that sepsis represents a major contributor to childhood morbidity and mortality and the associated economic burden. The United Nations Sustainable Development Goal 3 (https://sustainabledevelopment.un.org/sdg3) defined specific targets for infections and pandemics.[2] Despite the huge burden that sepsis imposes on the health of children,[3,4] current definitions of pediatric sepsis are of limited value to bedside clinicians to identify cases of sepsis. Moreover, these definitions have poor predictive value and have not been validated, thus lessening their utility in

sence of a criterion standard, the Adult Sepsis Definition Taskforce has operationalized sepsis definitions that were developed and validated in large cohorts using a data-driven approach rather than expert consensus alone.[6] The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) definition[6] emphasizes 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. Septic shock is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Using the Sequential Organ Failure Assessment (SOFA) score, patients with new organ dysfunction are identified. The paradigm change in content and

In conclusion, there is thus an urgent need to translate Sepsis-3 into definitions adapted for the specific disease characteristics, susceptibilities, and patterns of pediatric sepsis. Failure to re-

recognition of and intervention for sepsis, with an emphasis on a clinician-defined spectrum of disease. Presumed or proven infection with systemic inflammation (SIRS) was defined as sepsis, with progressive organ dysfunction defined as severe sepsis and cardiovascular dysfunction as septic shock. However, SIRS is very commonly manifested in otherwise well febrile children, and even in children without infections, leading to low specificity and thus limited use to clinicians.[5] During the winter months, more than half the population of children in emergency departments present with runny noses due to viral infections, which would satisfy the present criteria for sepsis. Apart from the stress on resources even in high-income countries, many health care facilities in low- and middle-income countries do not have the resources to perform white blood cell counts (a requirement for

created some anxiety as to how it will be used, especially in low- and middle-income countries.[7]

The Sepsis-3 consensus statement was designed for adults and the task force recognized "the need to develop similar updated definitions for pediatric populations."[6(p808)] Although the SOFA score was not designed for pediatric age groups, several recent studies have demonstrated, in principle, the feasibility of applying Sepsis-3–based criteria to pediatric age groups.[5,8] Translating Sepsis-3 criteria into pediatrics will require taking age-related differences in pathophysiology and clinical manifestations into account. For example, arterial hypotension, which is 1 of 3 essential criteria for septic shock in adults, represents a generally late sign of septic shock in children.[9] Furthermore, the fulminant nature often seen in community-acquired pediatric sepsis will

JAMA Pediatrics | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children

Travis J. Matics, DO; L. Nelson Sanchez-Pinto, MD, MBI

JAMA Pediatrics | Original Investigation

Validation of the Pediatric Sequential Organ Failure Assessment Score and Evaluation of Third International Consensus Definitions for Sepsis and Septic Shock Definitions in the Pediatric Emergency Department

Fran Balamuth, MD, PhD; Halden F. Scott, MD, MSCS; Scott L. Weiss, MD, MSCE; Michael Webb, MS; James M. Chamberlain, MD; Lalit Bajaj, MD, MPH; Holly Depinet, MD, MPH; Robert W. Grundmeier, MD; Diego Campos, MS; Sara J. Deakyne Davies, MPH; Norma Jean Simon, MS; Lawrence J. Cook, PhD; Elizabeth R. Alpern, MD, MSCE; for the Pediatric Emergency Care Applied Research Network (PECARN) PED Screen and PECARN Registry Study Groups

International Pediatric Sepsis Definition Task Force

- Salzburg, 2019
- Agreement on conceptual definition: life threatening organ dysfunction caused by infection

Systematic Review

Menon K, et al. Criteria for Pediatric Sepsis – A Systematic Review and Meta-Analysis by the Pediatric Sepsis Definition Taskforce. Crit Care Med. 2022.

- Kusum Menon
- Luregn J. Schlapbach
- Samuel Akech
- Andrew Argent
- Paolo Biban
- Enitan D. Carrol
- Kathleen Chiotos
- Mohammod Jobayer Chisti
- Idris V.R. Evans
- David P. Inwald
- Paul Ishimine
- Niranjan Kissoon
- Rakesh Lodha
- Simon Nadel
- Claudio Flauzino Oliveira
- Mark Peters
- Benham Sadeghirad
- Halden F. Scott
- Daniela C. deSouza
- Pierre Tissieres
- R. Scott Watson
- Matthew O. Wiens
- James L. Wynn
- Jerry J. Zimmerman
- Lauren R. Sorce

on **behalf of the Society of Critical Care Medicine's Pediatric Sepsis Definition Taskforce**

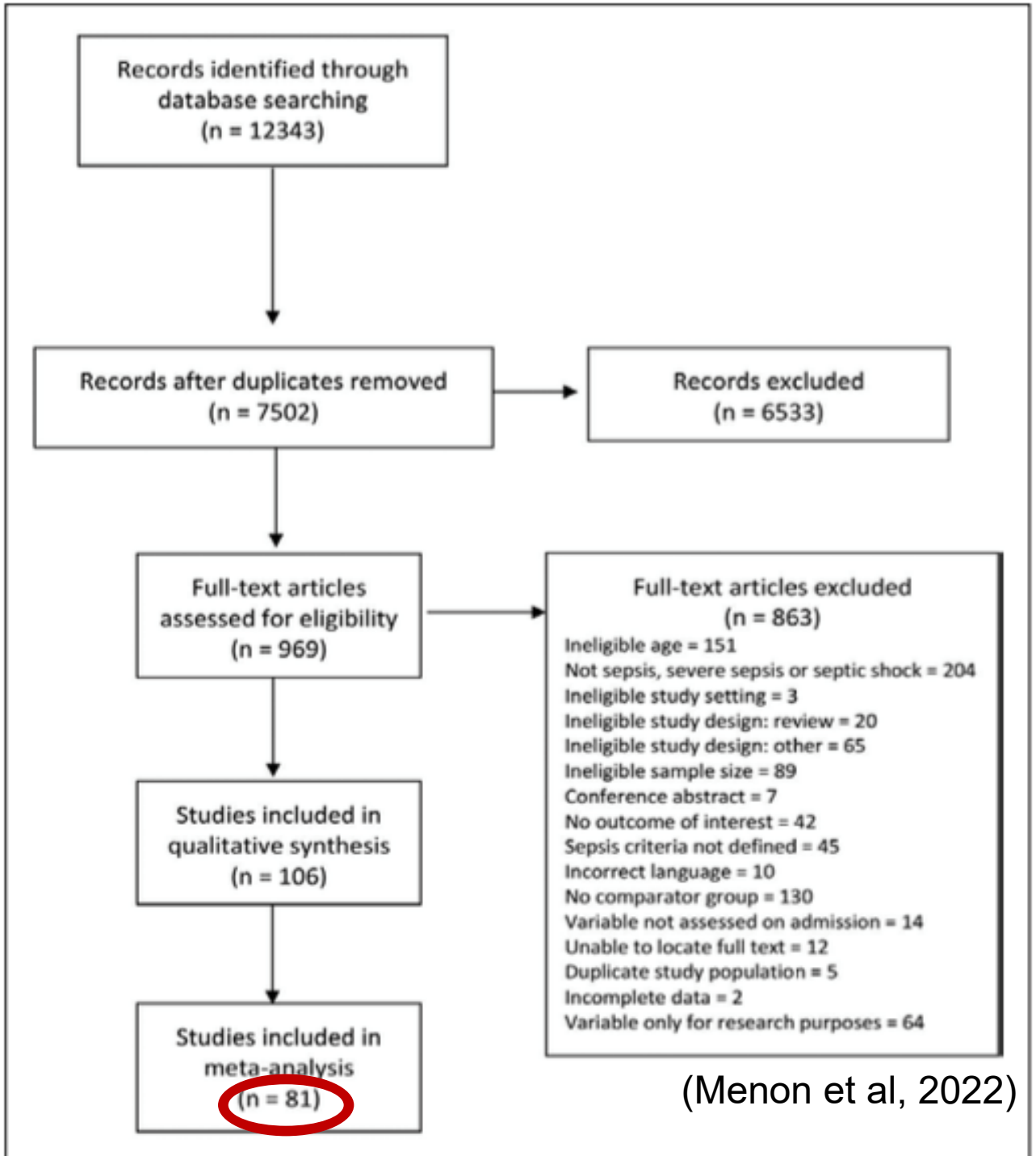
Aims

To determine the associations of variables with

1) **Sepsis, severe sepsis, or septic shock** in children with infection
2) **Multiple organ dysfunction or death** in children with sepsis, severe sepsis, or septic shock

Evaluating the following variable domains:

- Demographic
- Clinical
- Laboratory
- Organ dysfunction
- Illness severity



(Menon et al, 2022)

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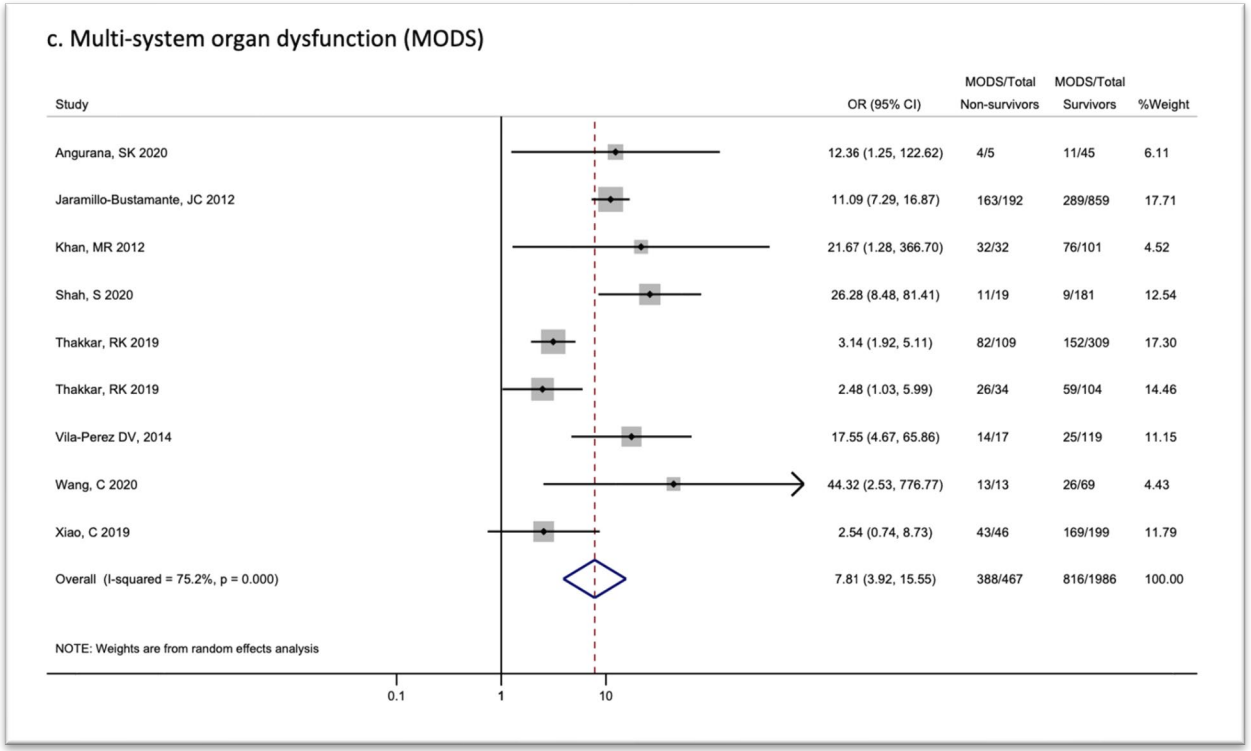
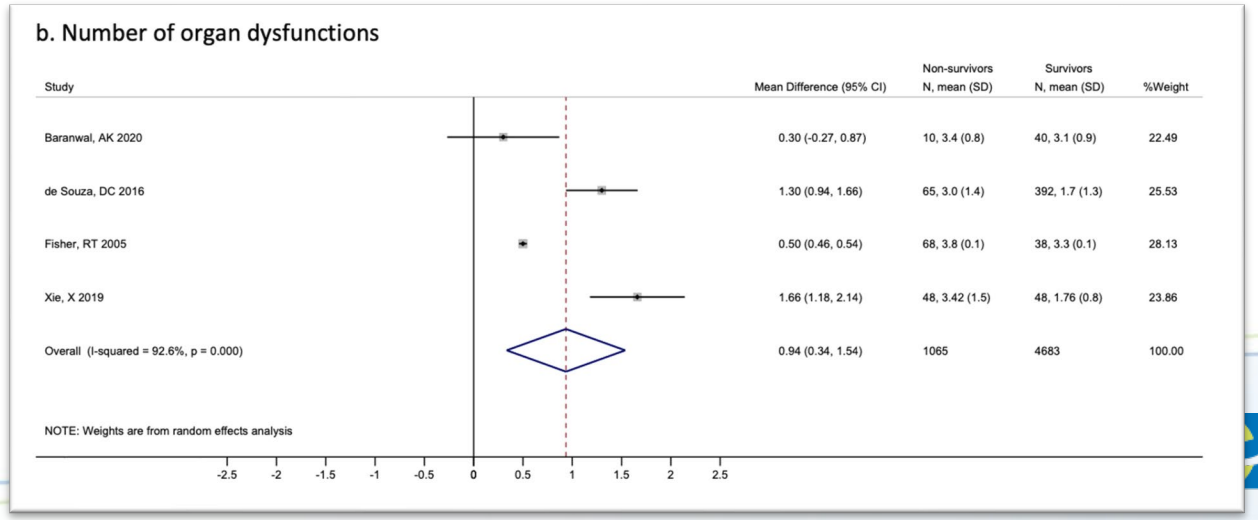
Results

SURVIVORS NON-SURVIVORS





(Menon et al, 2022)

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Results

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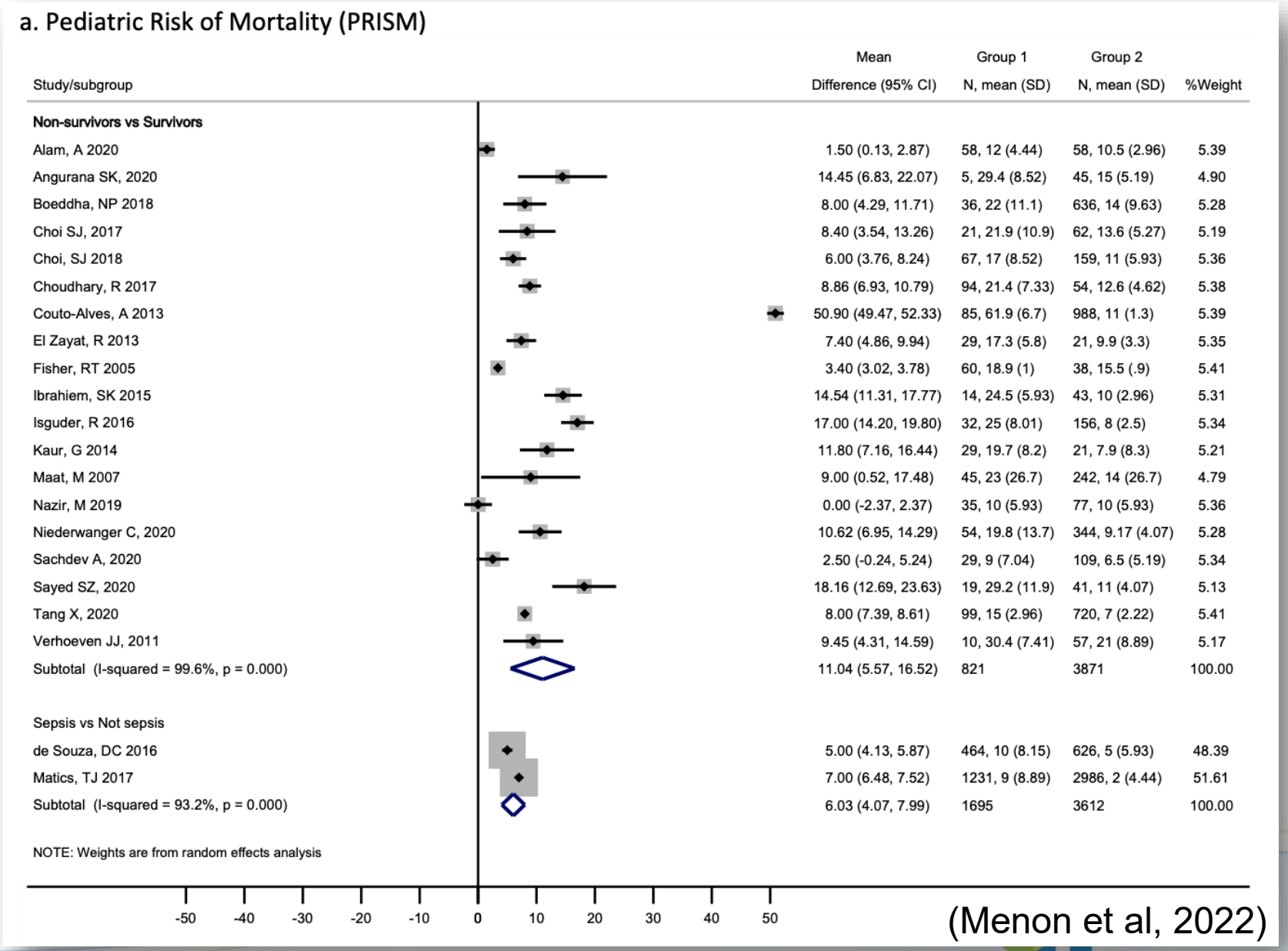


(Menon et al, 2022)

Discussion: Two Aims

Criteria associated with sepsis among children with infection

- Few identified
- Search strategy and existing research
  - Pediatric febrile illness studies not included unless they contained a defined sepsis population
  - Reflects different outcomes used in research in non-ICU (bacterial infection, hospitalization)

Criteria associated with mortality among children with sepsis

- Organ dysfunction CONCEPTS and SCORES are associated with mortality in pediatric sepsis
- Some organ dysfunctions more ominous than others

Discussion

Systematic review identified variables commonly measured, associated with mortality in sepsis across settings and varying sepsis definitions

Identified differences in country income contributed to

- Mortality differences
- Differences in representation of patients in the published literature

Ensured comprehensive search for variables important to include in data driven criteria selection process

International Survey

Drafted, revised, disseminated by Pediatric Sepsis Definition Taskforce

Distributed by 27 international societies (CCM, EM, ID, others)

English, Spanish, Portuguese, Mandarin and French

83 items

- Demographics
- Resource availability
- *Current* practice for sepsis diagnosis
- Viewpoint on usefulness of *current* sepsis definitions
- Viewpoint on goals for *new* sepsis definitions
- What should the word “sepsis” mean?

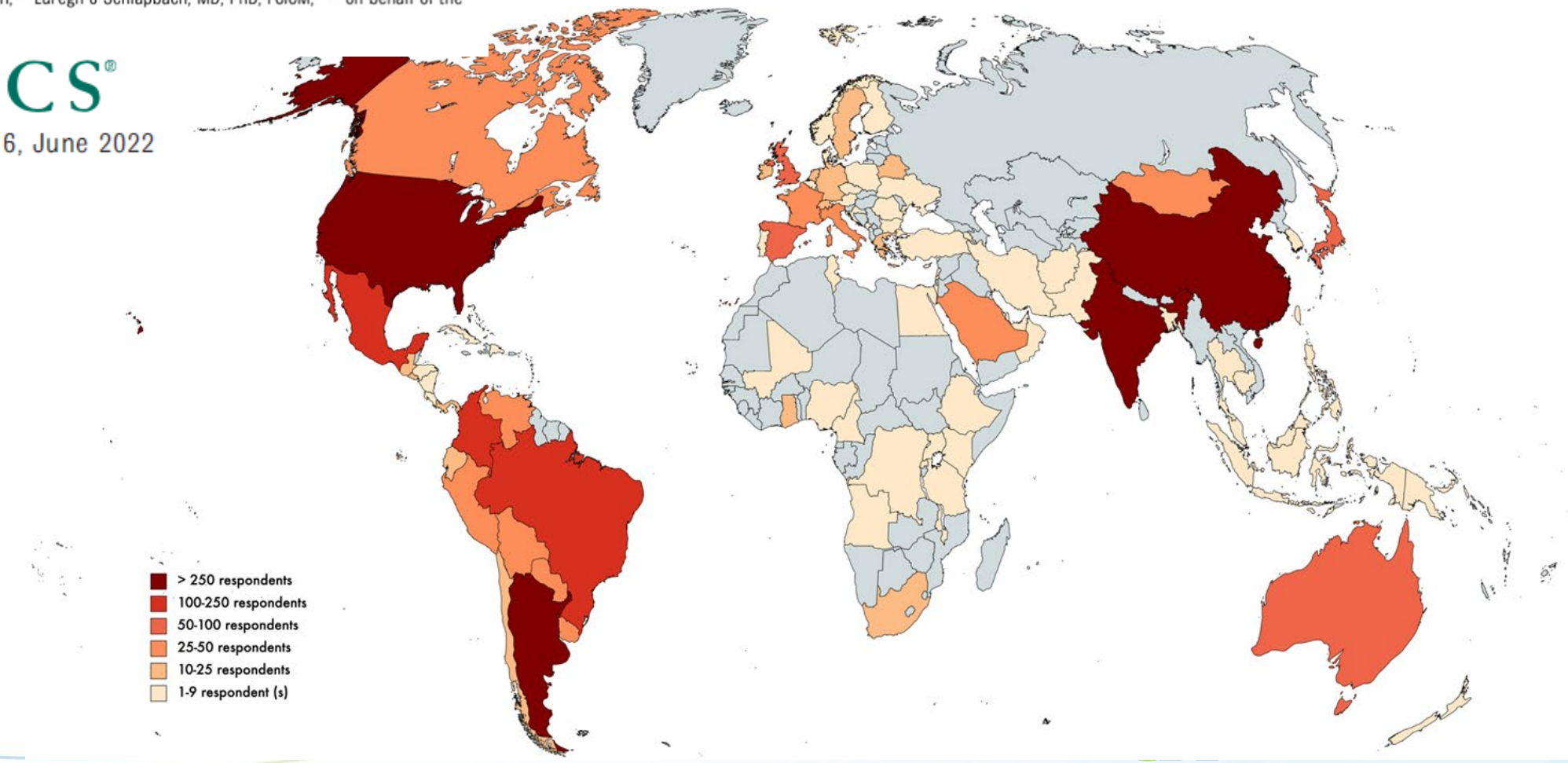
The Current and Future State of Pediatric Sepsis Definitions: An International Survey

Luc Morin, MD, MSc,[a] Mark Hall, MD,[b] Daniela de Souza, MD, PhD,[c,d] Lu Guoping, MD,[e] Roberto Jabornisky, MD,[f,g] Nobuaki Shime, MD,[h] Suchitra Ranjit, MD, FCCM,[i] Patricia Gilholm, PhD,[j] Satoshi Nakagawa, MD,[k] Jerry J. Zimmerman, MD, PhD,[l] Lauren R. Sorce, PhD, RN,[m,n] Andrew Argent, MBBCh, MD,[o,p] Niranjan Kissoon, MD,[q,r] Pierre Tissières, MD, DSc,[s,t] R. Scott Watson, MD, MPH,[l,*] Luregn J Schlapbach, MD, PhD, FCICM,[j,u,*] on behalf of the Pediatric Sepsis Definition Taskforce

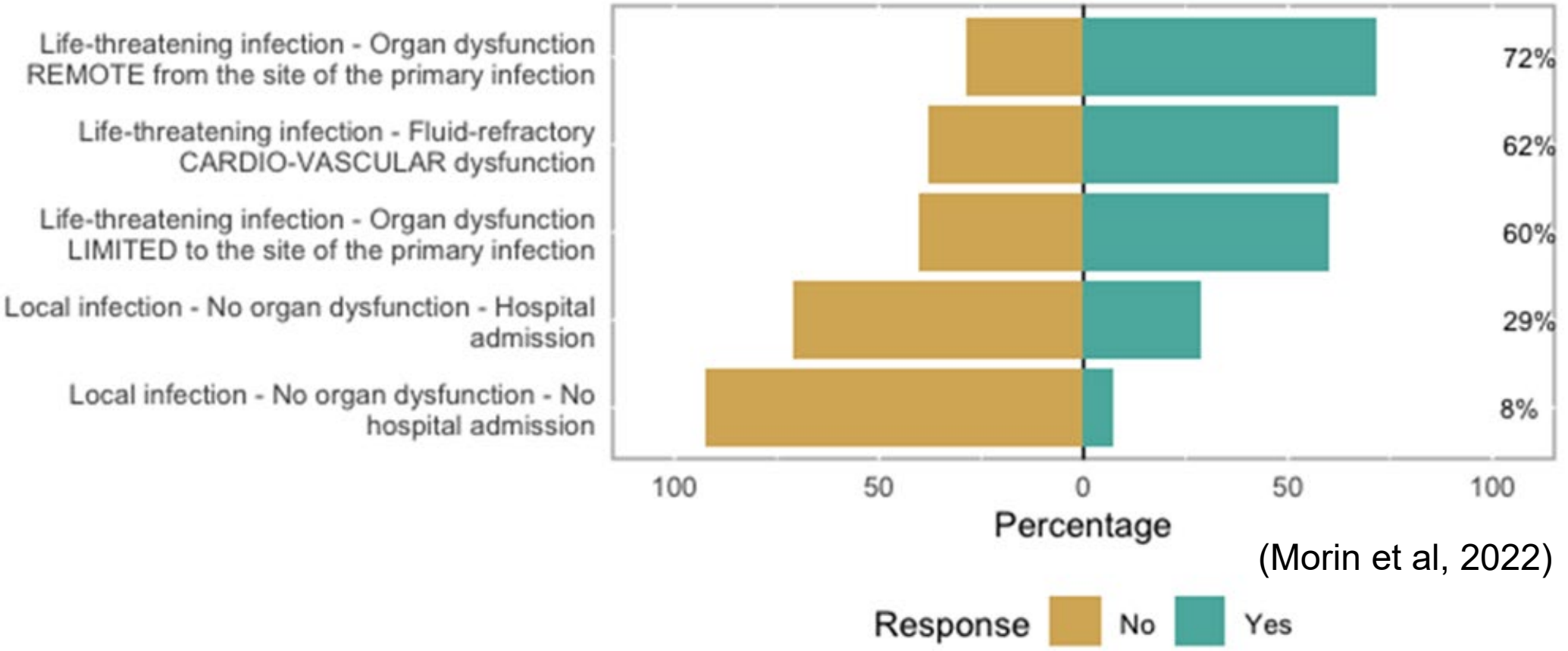
PEDIATRICS®

PEDIATRICS Volume 149, number 6, June 2022

2,835 analyzable responses



What should be called “sepsis”?



The answer is somewhere in here

(Morin et al, 2022)

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Use cases

Recognition	• Does this patient in front of me have sepsis?
Early recognition	• Is this patient developing sepsis?
Correct disease classification	• Did this/these patient(s) have sepsis?
Prognostication	• What is this patient's risk for adverse outcomes?
Benchmarking	• How good are we at diagnosing/managing sepsis?
Epidemiology	• Who/What/Where/When?
Enrollment in studies	• Understanding sepsis biology, clinical trials

Conclusions

The international community of clinicians who care for children with life-threatening infection:

- Has limits on the availability of diagnostic and therapeutic resources, but vital sign measurement and basic laboratory testing are frequently available
- Perceives current sepsis definitions to be inadequate for use across the spectrum of need (e.g. recognition, quality benchmarking, research)
- *Wants* a set of definitions that does it all!
- Is not unanimous on what the word “sepsis” should mean, but believe that it should be applied to life-threatening disease

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Phoenix Criteria

Chris Horvat, MD MHA

UPMC Children's Hospital of Pittsburgh

Research

JAMA | Original Investigation

Development and Validation of the Phoenix Criteria for Pediatric Sepsis and Septic Shock

L. Nelson Sanchez-Pinto, MD, MBI; Tellen D. Bennett, MD, MS; Peter E. DeWitt, PhD; Seth Russell, MS; Margaret N. Rebull, MA; Blake Martin, MD; Samuel Akech, MBChB, MMED; David J. Albers, PhD; Elizabeth R. Alpern, MD, MSCE; Fran Balamuth, MD, PhD, MSCE; Melania Bembea, MD, MPH, PhD; Mohammod Jobayer Chisti, MBBS, MMed, PhD; Idris Evans, MD, MSc; Christopher M. Horvat, MD, MHA; Juan Camilo Jaramillo-Bustamante, MD; Niranjan Kissoon, MD; Kusum Menon, MD, MSc; Halden F. Scott, MD, MSCS; Scott L. Weiss, MD; Matthew O. Wiens, PharmD, PhD; Jerry J. Zimmerman, MD, PhD; Andrew C. Argent, MD, MBBCh, MMed; Lauren R. Sorce, PhD, RN, CPNP-AC/PC; Luregn J. Schlapbach, MD, PhD; R. Scott Watson, MD, MPH; and the Society of Critical Care Medicine Pediatric Sepsis Definition Task Force

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Table 2. The Phoenix Sepsis Score[a]

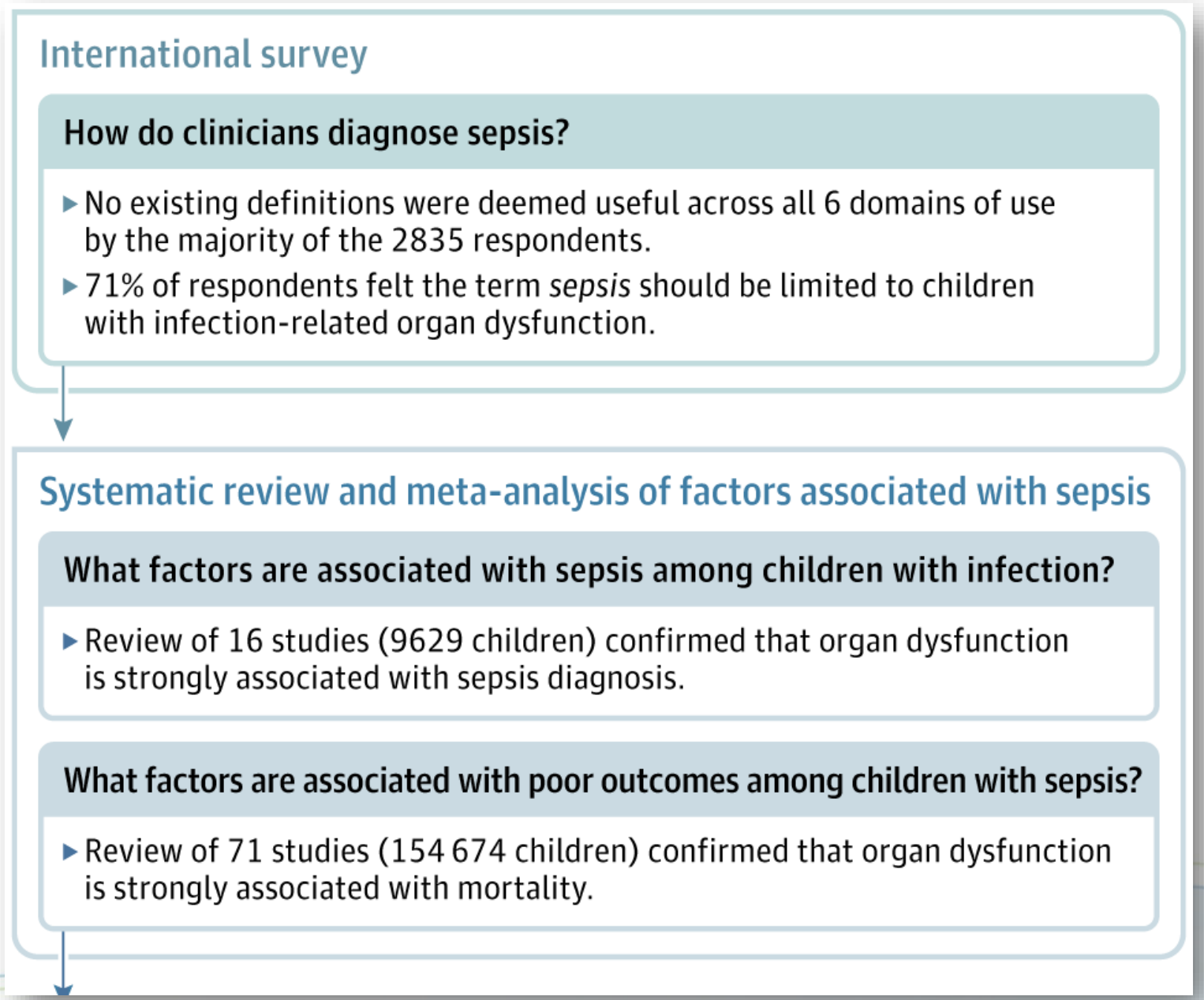
	0 Points	1 Point	2 Points	3 Points
Respiratory (0-3 points)				
	Pao_2:Fio_2 ≥400 *or* Spo_2:Fio_2 ≥292[b]	Pao_2:Fio_2 <400 and any respiratory support[c] *or* Spo_2:Fio_2 <292 and any respiratory support[c]	Pao_2:Fio_2 100-200 and IMV *or* Spo_2:Fio_2 148-220 and IMV	Pao_2:Fio_2 <100 and IMV *or* Spo_2:Fio_2 <148 and IMV
Cardiovascular (0-6 points)				
		1 point each (up to 3) for:	2 points each (up to 6) for:	
	No vasoactive medications[d]	1 Vasoactive medication[d]	≥2 Vasoactive medications[d]	
	Lactate <5 mmol/L[e]	Lactate 5-10.9 mmol/L[e]	Lactate ≥11 mmol/L[e]	
Mean arterial pressure by age, mm Hg[f,g]				
<1 mo	>30	17-30	<17	
1 to 11 mo	>38	25-38	<25	
1 to <2 y	>43	31-43	<31	
2 to <5 y	>44	32-44	<32	
5 to <12 y	>48	36-48	<36	
12 to 17 y	>51	38-51	<38	
Coagulation (0-2 points)[h]				
		1 point each (maximum of 2 points) for:		
	Platelets ≥100 × 10^3/μL	Platelets <100 × 10^3/μL		
	International normalized ratio ≤1.3	International normalized ratio >1.3		
	D-dimer ≤2 mg/L FEU	D-dimer >2 mg/L FEU		
	Fibrinogen ≥100 mg/dL	Fibrinogen <100 mg/dL		
Neurologic (0-2 points)[i]				
	Glasgow Coma Scale score >10[j]; pupils reactive	Glasgow Coma Scale score ≤10[j]	Fixed pupils bilaterally	

(Sanchez-Pinto et al., 2024)

EDITORIAL

Context and Implications of the New Pediatric Sepsis Criteria

Erin F. Carlton, MD, MSc; Mallory A. Perry-Eaddy, PhD, RN; Hallie C. Prescott, MD, MSc



Sepsis

Infection with life-threatening organ dysfunction

EDITORIAL

Context and Implications of the New Pediatric Sepsis Criteria

Erin F. Carlton, MD, MSc; Mallory A. Perry-Eaddy, PhD, RN; Hallie C. Prescott, MD, MSc

Cohort study to develop and validate pediatric sepsis criteria

For each of 8 organ systems, which existing criteria best predict hospital mortality?

- The best performing criteria were identified for each of 8 individual organ systems, from 5 existing scoring systems: International Pediatric Sepsis Consensus Conference (IPSCC), Pediatric Logistic Organ Dysfunction (PELOD-2), Pediatric Organ Dysfunction Information Update Mandate (PODIUM), pediatric SOFA, and Proulx.

Which organ system dysfunctions best predict hospital mortality among children with infection?

- A 4-system model including cardiovascular, coagulation, neurologic, and respiratory systems achieved similar discrimination as the full 8-system model.

Taskforce consensus process

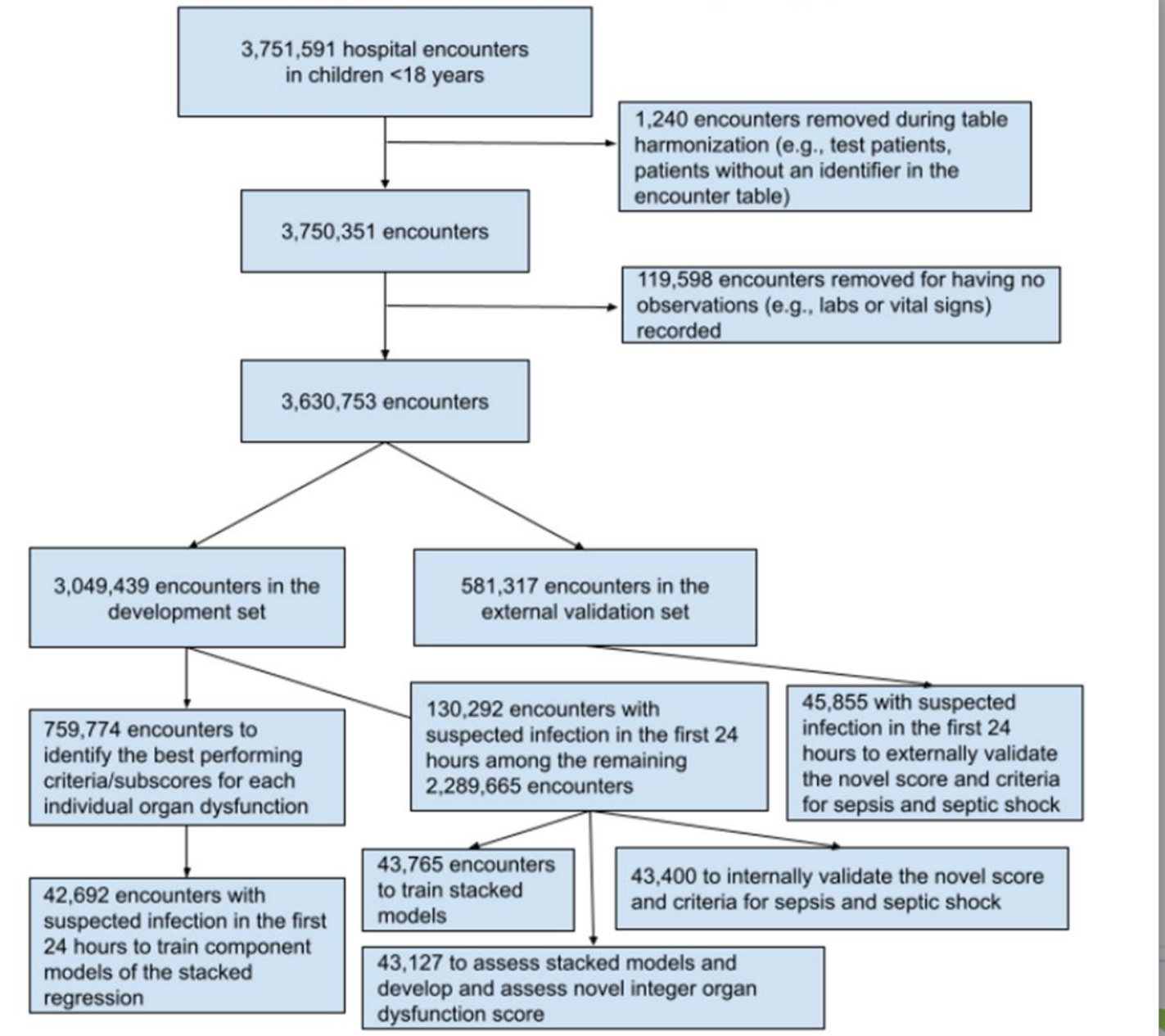
How should pediatric sepsis be identified in practice?

- The 4-system model was prioritized for clinical use and converted to Phoenix Sepsis Score.
- Septic shock requires ≥1 point in the cardiovascular system.
- The 8-system model may be useful for research and was converted to Phoenix-8 Score.

Methods

- Retrospective cohort study using EHR data from 10 hospitals across 5 countries
- Primary outcome was in-hospital mortality
- Suspected infection = systemic antimicrobials and microbiological testing within the first 24 hours of the encounter
- AUPRC was primary measure of the organ dysfunction subscore
- Pre-specified strata, including high vs low resource country

B. CONSORT-style flow diagram for encounters in the various analyses



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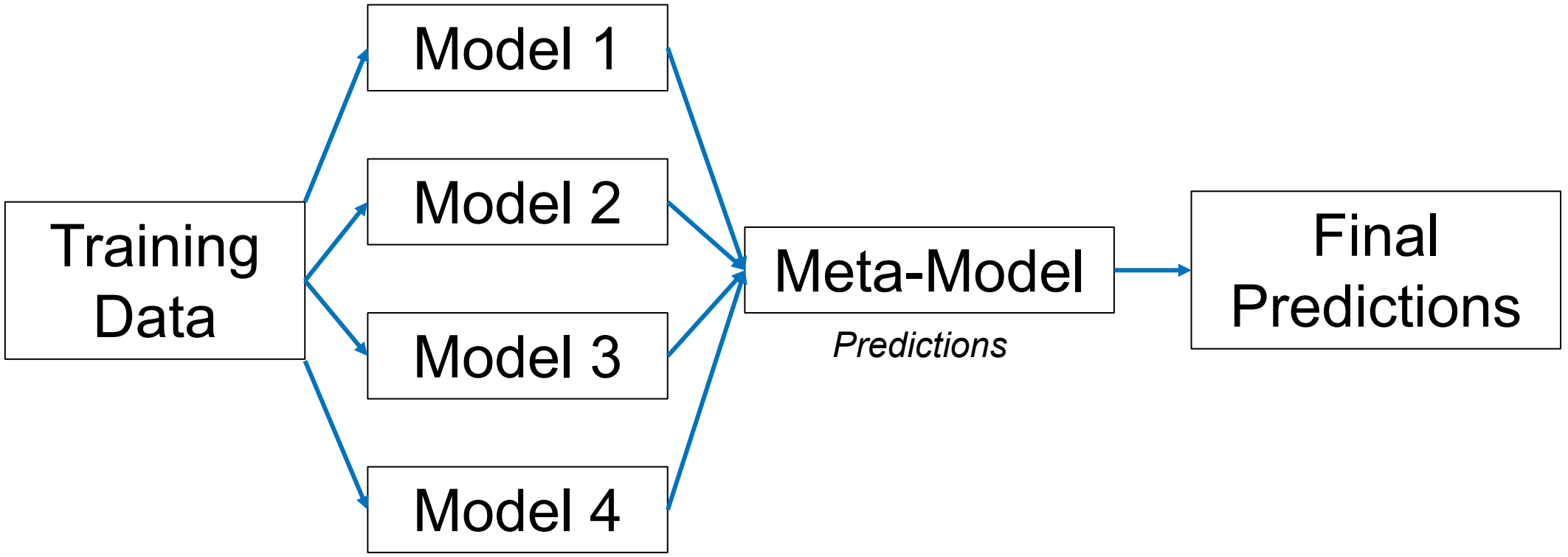
What is stacked regression?



eFigure 1. Conceptual illustration of how stacked regression was used to develop the sepsis criteria

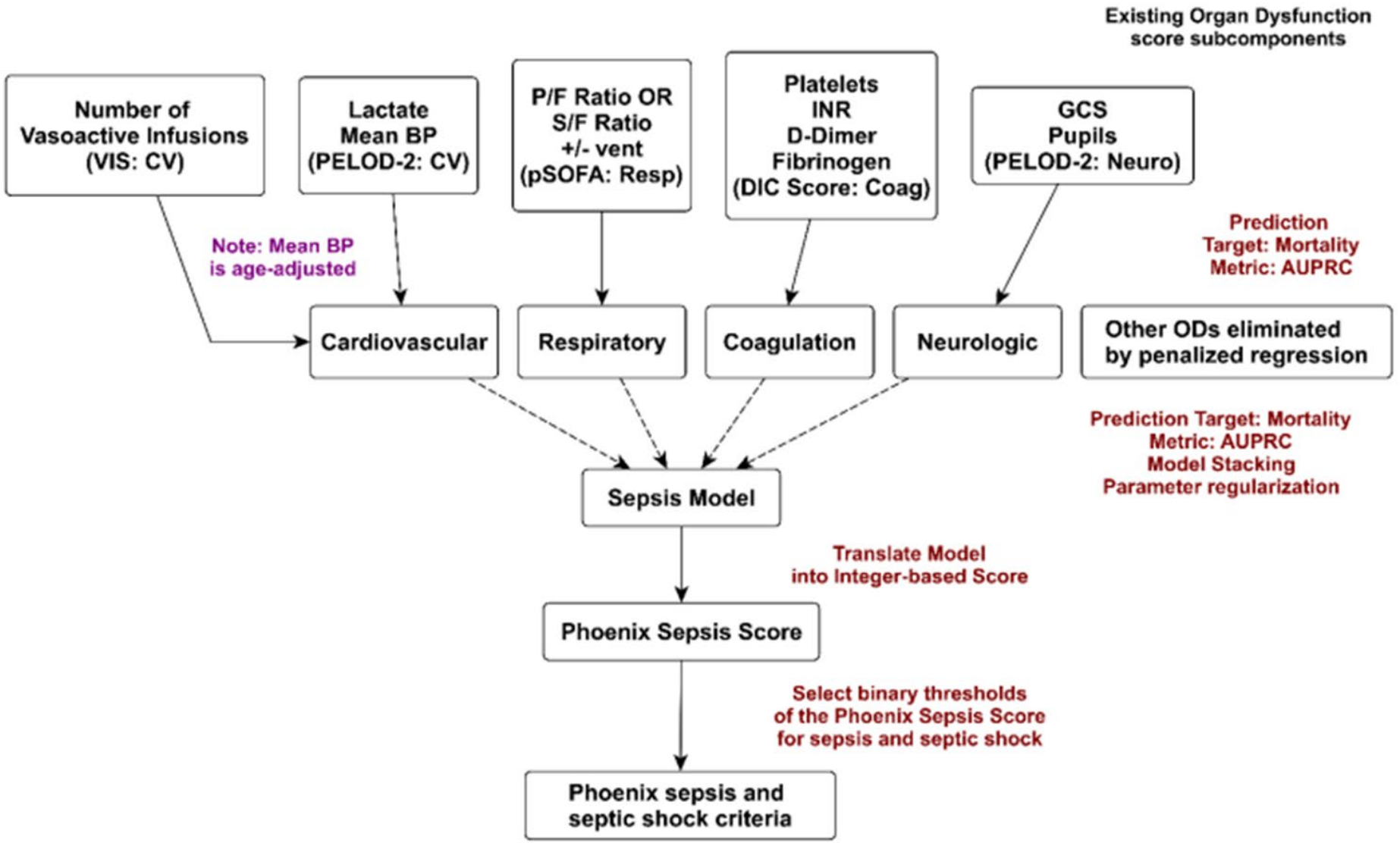


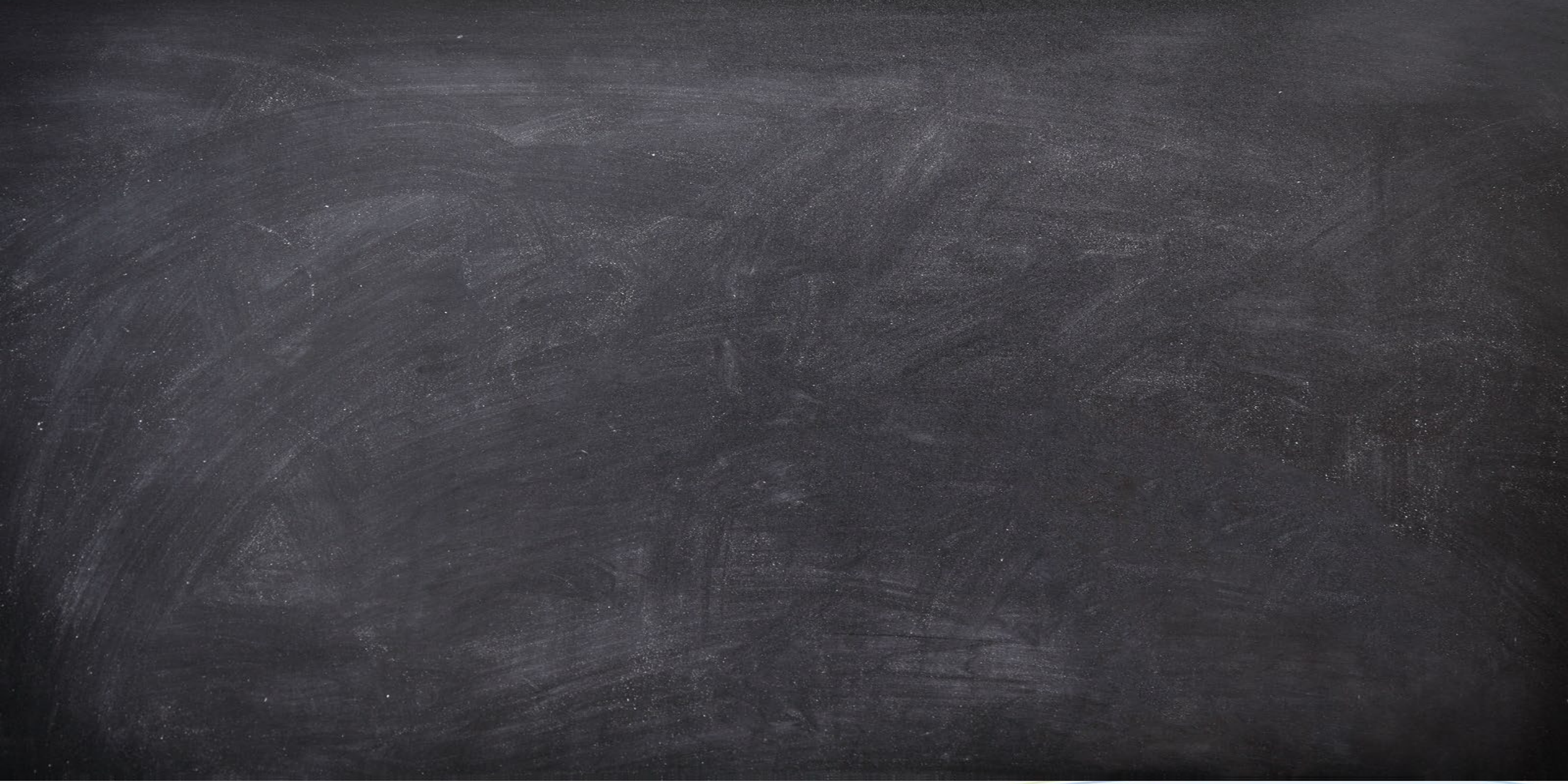
Figure 3. Mortality Prediction Performance of the Phoenix Sepsis Score and Organ Dysfunction Scores

A Area under the precision recall curve (AUPRC)

	Internal validation set						
	Phoenix sepsis	IPSCC	Phoenix-8	PELOD-2	pSOFA	Proulx	PODIUM
Higher-resource sites 1-5	0.28 (0.27-0.28)	0.16 (0.16-0.16)	0.28 (0.27-0.28)	0.30 (0.30-0.31)	0.17 (0.17-0.18)	0.22 (0.22-0.22)	0.20 (0.20-0.21)
Lower-resource site 1	0.37 (0.35-0.39)	0.18 (0.16-0.20)	0.33 (0.31-0.35)	0.22 (0.20-0.24)	0.27 (0.25-0.29)	0.25 (0.23-0.27)	0.24 (0.23-0.26)
Lower-resource site 2	0.31 (0.30-0.32)	0.27 (0.26-0.28)	0.34 (0.32-0.35)	0.16 (0.15-0.17)	0.33 (0.32-0.34)	0.20 (0.19-0.22)	0.24 (0.22-0.25)
	External validation set						
Higher-resource site 6	0.38 (0.37-0.38)	0.16 (0.15-0.16)	0.37 (0.36-0.37)	0.35 (0.34-0.35)	0.20 (0.20-0.21)	0.21 (0.20-0.21)	0.22 (0.21-0.22)
Lower-resource site 3	0.26 (0.24-0.28)	0.15 (0.13-0.16)	0.23 (0.21- 0.24)	0.16 (0.14- 0.18)	0.14 (0.13-0.16)	0.16 (0.15-0.18)	0.13 (0.12-0.15)
Lower-resource site 4	0.23 (0.22-0.24)	0.13 (0.13-0.14)	0.20 (0.19-0.206)	0.11 (0.10-0.12)	0.18 (0.18-0.19)	0.15 (0.14-0.15)	0.11 (0.11-0.12)
All sites (internal and external validation sets)	0.21 (0.20-0.21)	0.12 (0.12-0.12)	0.20 (0.20-0.21)	0.18 (0.18- 0.18)	0.15 (0.15-0.15)	0.15 (0.15-0.15)	0.14 (0.14-0.14)

B Area under the receiver operating characteristic curve (AUROC)

	Internal validation set						
	Phoenix sepsis	IPSCC	Phoenix-8	PELOD-2	pSOFA	Proulx	PODIUM
Higher-resource sites 1-5	0.88 (0.88-0.88)	0.88 (0.88-0.88)	0.91 (0.90-0.91)	0.86 (0.86-0.87)	0.90 (0.89-0.90)	0.86 (0.85-0.86)	0.89 (0.89-0.90)
Lower-resource site 1	0.91 (0.90-0.92)	0.85 (0.83-0.86)	0.90 (0.89-0.91)	0.84 (0.83-0.86)	0.89 (0.87-0.90)	0.90 (0.89-0.91)	0.77 (0.75-0.79)
Lower-resource site 2	0.71 (0.70-0.72)	0.78 (0.77-0.80)	0.85 (0.84-0.86)	0.78 (0.77- 0.79)	0.83 (0.82-0.84)	0.72 (0.70-0.73)	0.78 (0.77-0.79)
	External validation set						
Higher-resource site 6	0.92 (0.92-0.92)	0.91 (0.91-0.92)	0.94 (0.94-0.94)	0.92 (0.92-0.92)	0.93 (0.93-0.93)	0.91 (0.91-0.91)	0.92 (0.91-0.92)
Lower-resource site 3	0.81 (0.80-0.83)	0.76 (0.74-0.78)	0.78 (0.76-0.79)	0.70 (0.67-0.71)	0.73 (0.71-0.75)	0.71 (0.69-0.73)	0.71 (0.69-0.73)
Lower-resource site 4	0.80 (0.79-0.81)	0.81 (0.80-0.81)	0.80 (0.79-0.80)	0.73 (0.72-0.74)	0.82 (0.81- 0.83)	0.74 (0.73-0.75)	0.75 (0.74-0.76)
All sites (internal and external validation sets)	0.82 (0.82-0.83)	0.83 (0.83-0.84)	0.87 (0.87-0.87)	0.80 (0.80-0.81)	0.86 (0.86-0.87)	0.81 (0.81-0.81)	0.84 (0.83-0.84)



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RESEARCH ARTICLE

The Precision-Recall Plot Is More Informative than the ROC Plot When Evaluating Binary Classifiers on Imbalanced Datasets

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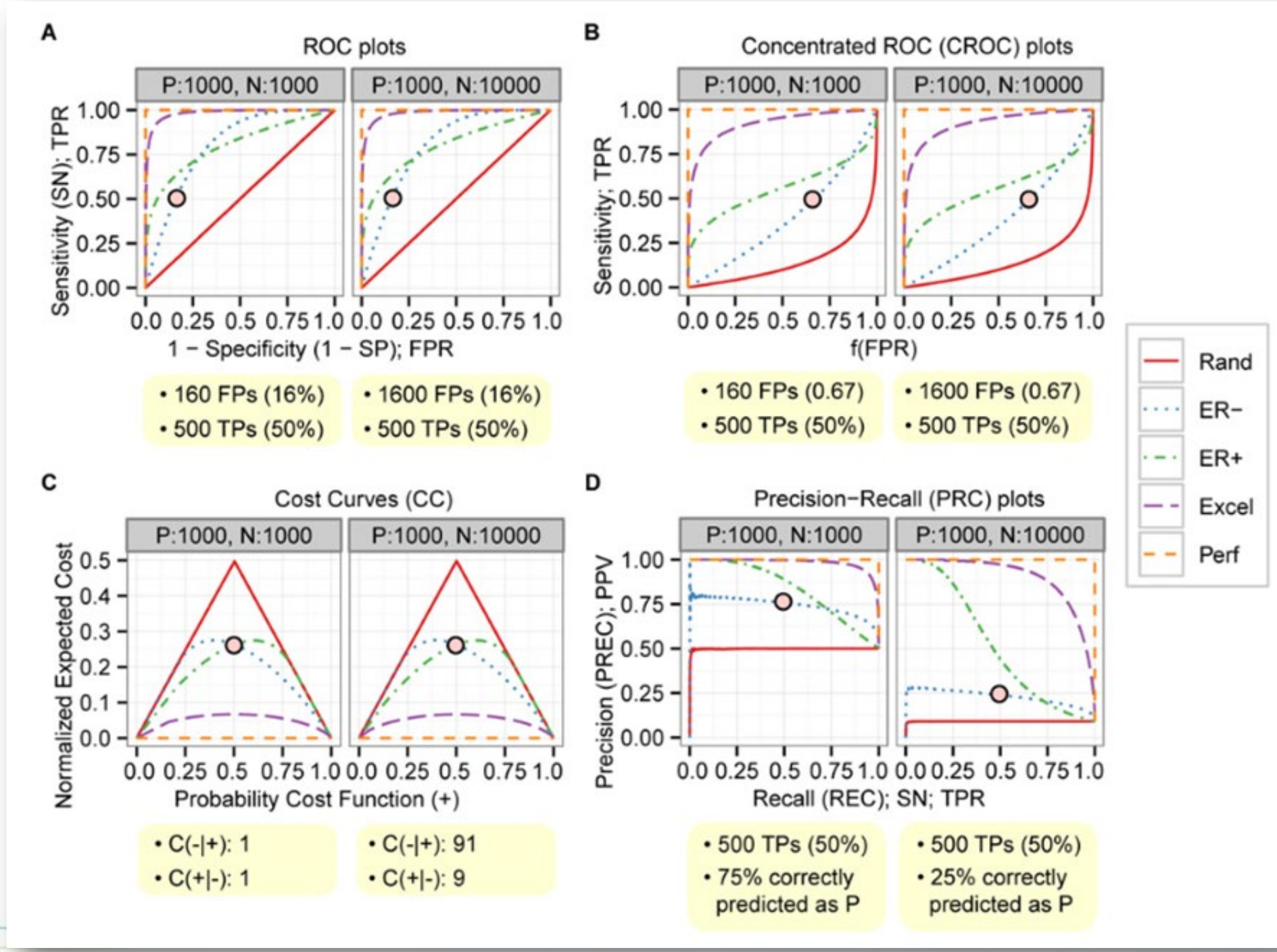

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Citation: Saito T, Rehmsmeier M (2015) The Precision-Recall Plot Is More Informative than the ROC Plot When Evaluating Binary Classifiers on Imbalanced Datasets. PLoS ONE 10(3): e0118432. doi:10.1371/journal.pone.0118432

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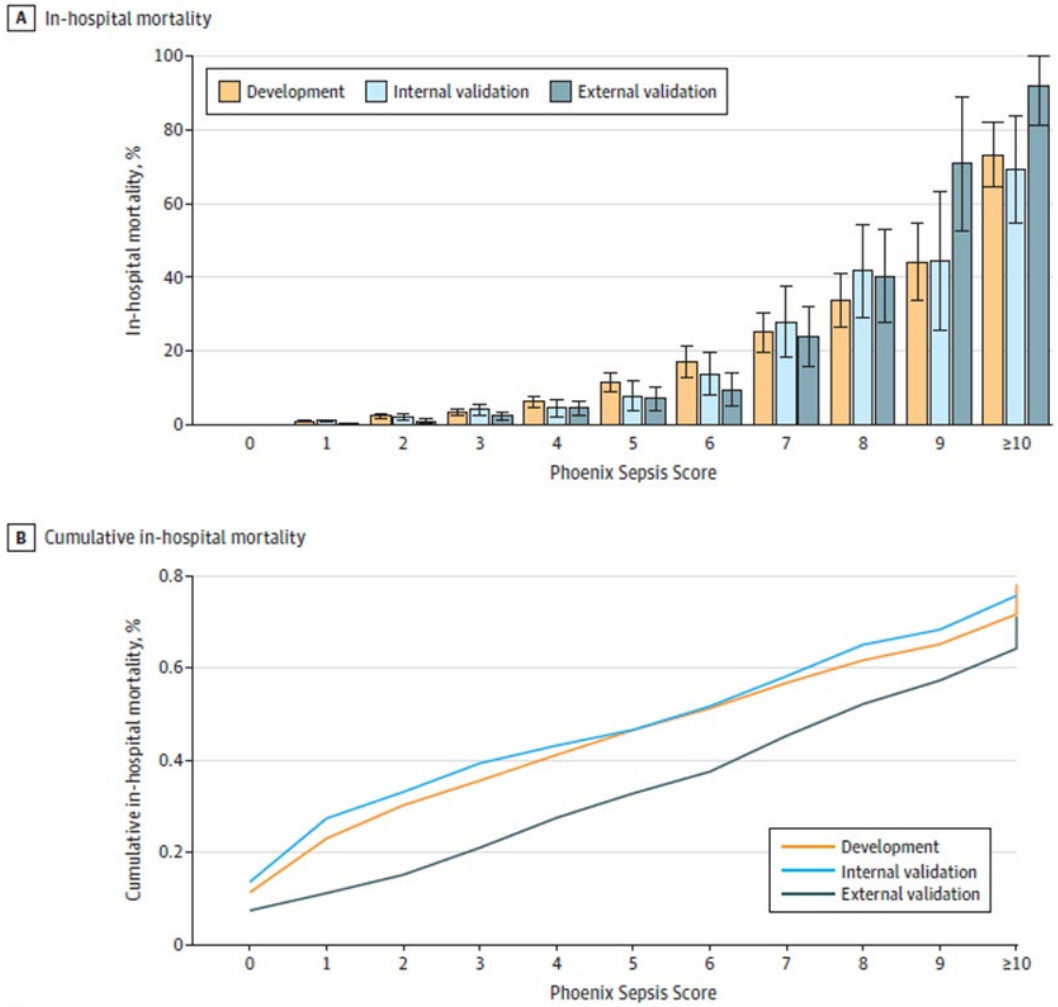
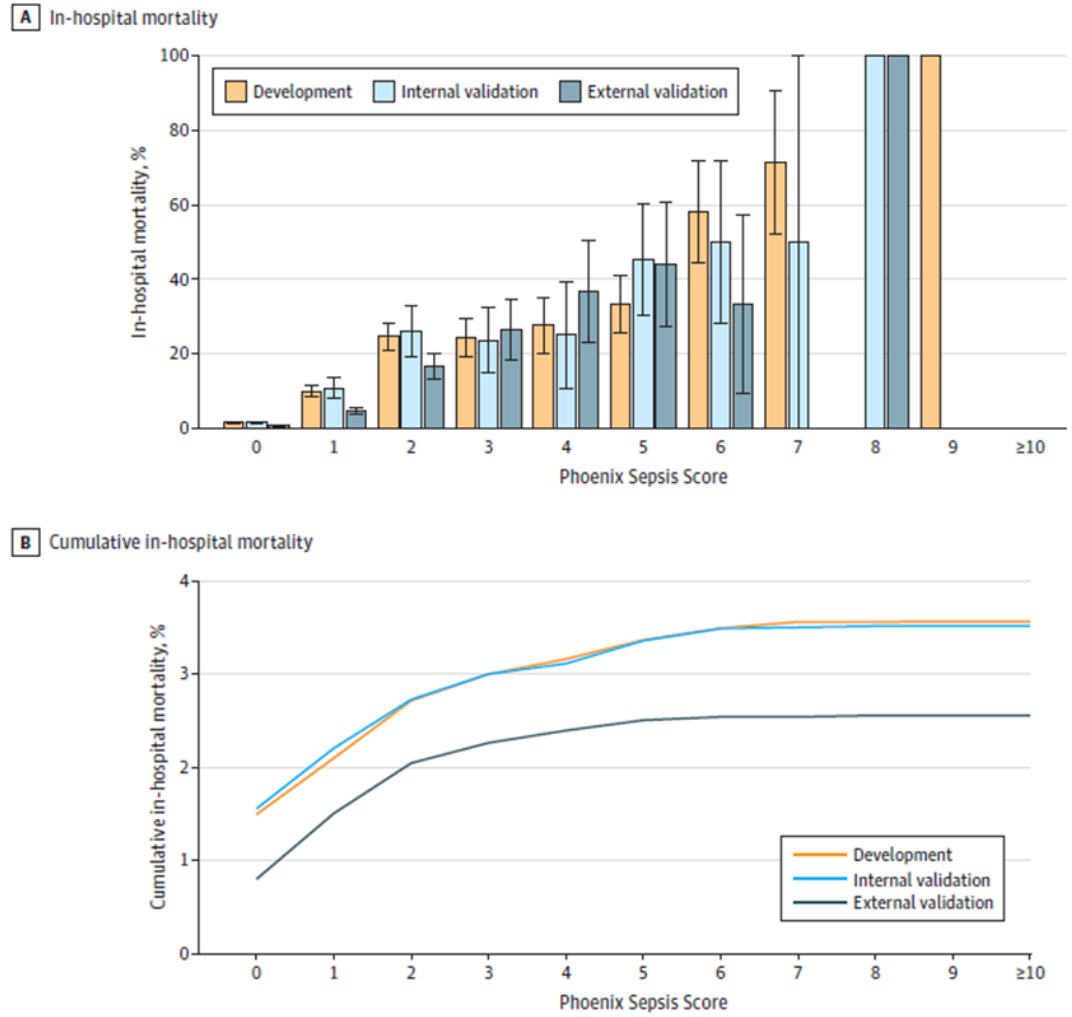
Figure 1. In-Hospital Mortality Associated With the Phoenix Sepsis Score in Patients in Higher-Resource Settings With Suspected Infection in the First 24 Hours



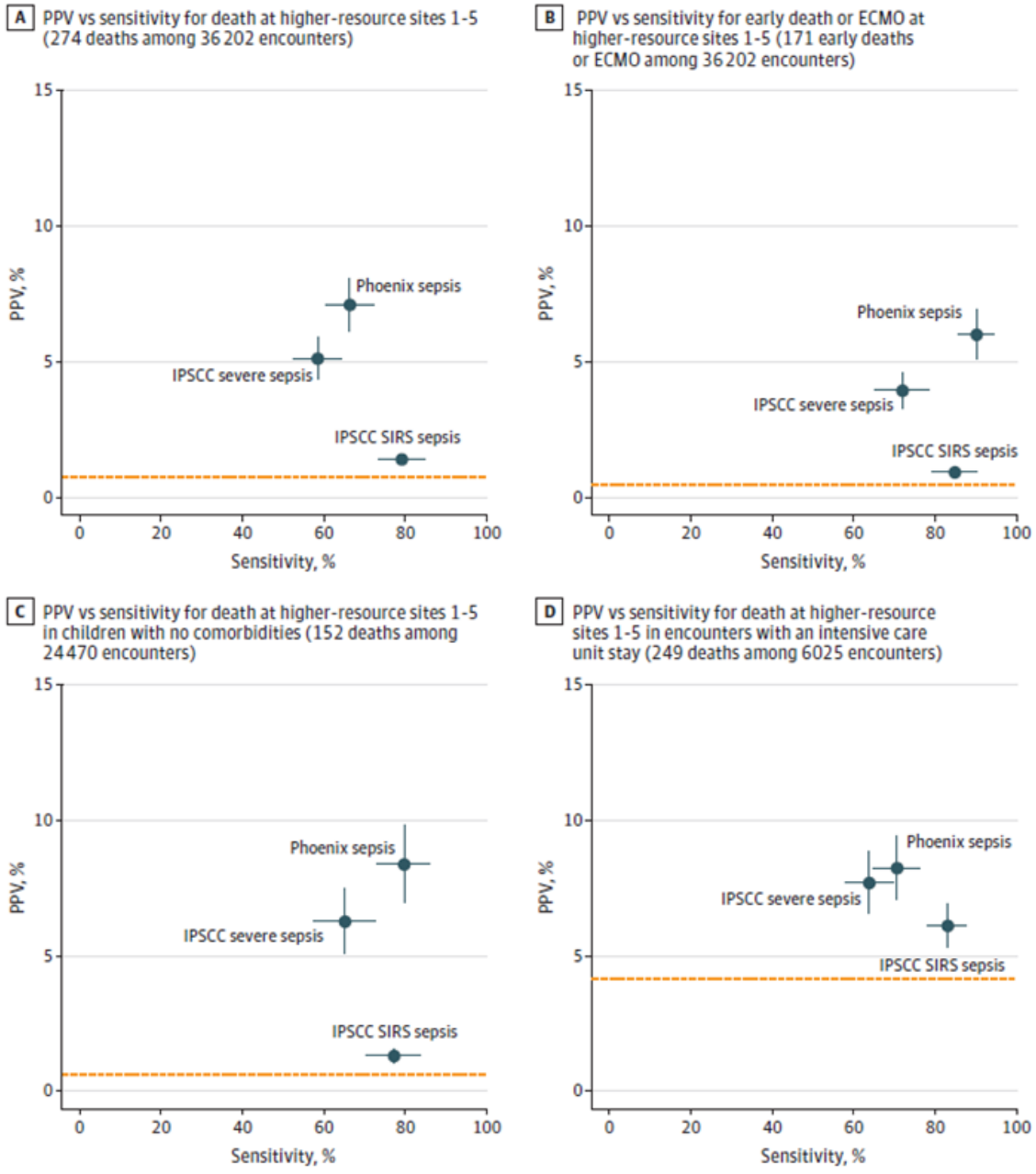
No. of events											
Development											
Encounters	85947	14545	3479	1775	1018	522	304	244	160	86	97
In-hospital mortality	97	134	83	62	63	60	52	61	54	38	71
Internal validation											
Encounters	28760	4884	1119	590	333	166	138	86	60	27	39
In-hospital mortality	39	53	23	24	15	13	19	24	25	12	27
External validation											
Encounters	24426	5222	1443	822	474	251	167	109	57	24	25
In-hospital mortality	18	15	14	20	22	18	16	26	23	17	23

Figure 2. In-Hospital Mortality Associated With the Phoenix Sepsis Score in Patients in Lower-Resource Settings With Suspected Infection in the First 24 Hours



No. of events											
Development											
Encounters	18754	1452	568	275	141	144	50	21	1	1	0
In-hospital mortality	280	144	140	67	39	48	29	15	0	1	0
Internal validation											
Encounters	6368	482	154	93	36	42	20	2	1	0	0
In-hospital mortality	99	52	40	22	9	19	10	1	1	0	0
External validation											
Encounters	10021	2146	453	114	49	34	15	1	2	0	0
In-hospital mortality	80	103	75	30	18	15	5	0	2	0	0

Figure 4. Comparison of Sensitivity and PPV of Novel Phoenix Sepsis Criteria With Current IPSCC Sepsis and Severe Sepsis Criteria Across Outcomes and Patient Subgroups in the Internal Validation Sets



Key Takeaways

1. The Phoenix criteria were derived using data from 3.6 million pediatric sepsis encounters
   - Data were from both higher and lower resource settings

2. The Phoenix criteria were derived and validated to predict ***mortality*** in children with suspected infection

3. The Phoenix criteria demonstrated superior performance based on AUPRC compared to other organ dysfunction scores and previous sepsis criteria

What are the Phoenix criteria NOT?

- **NOT** a screening tool for children with early indications of life-threatening infections
- **NOT** a tool for determining when to perform a workup for infections (e.g., obtain blood or other body fluid cultures)
- **NOT** a tool for determining when to give antibiotics
- **NOT** a tool for determining when to give fluids
- **NOT** a tool for determining when to administer vasoactive medications
- **NOT** comprehensive criteria for multiple organ dysfunction

The monumental achievements of the Improving Pediatric Sepsis Outcomes (IPSO) collaborative

1. EHR-based definitions of sepsis
   - 8 cascading sets of criteria
2. Implementing screening and management pathways focused on early recognition of sepsis:
   - 35.7% reduction in mortality among children with suspected sepsis
   - 49.5% reduction in mortality among children with critical sepsis

(Scott et al, 2020; Larsen et al, 2021; Paul et al, 2023)

How is our site incorporating the Phoenix criteria?

- Prevention is better than cure! (*Desiderus Erasmus, ~1500*)

- Vigilance still required across 3 core domains:
  1. Recognition and treatment of the specific pathogen
  2. Addressing the individual child's biomolecular response to infection
  3. Promoting optimal systems of care delivery

Thank you

Questions?

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Controversies

Slides courtesy of Tell Bennet and Nelson Sanchez-Pinto and SCCM Taskforce

Why use existing organ dysfunction subcomponents in Step 1?

- Already validated in children
- Community has experience with them
- Pragmatic approach

Slide courtesy of SCCM/Bennet/Sanchez-Pinto

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Organ system	Organ Dysfunction Score/Criteria							
	IPSCC	PELOD-2	PODIUM	Proulx	pSOFA	DIC	VIS	SI
Cardiovascular	X	X	X	X	X		X	X
Respiratory	X	X	X	X	X			
Neurological	X	X	X	X	X			
Renal	X	X	X	X	X			
Hepatic	X		X	X	X			
Heme/Coag	X	X	X	X	X	X		
Immunologic			X					
Endocrine			X					

Slide courtesy of SCCM/Bennet/Sanchez-Pinto

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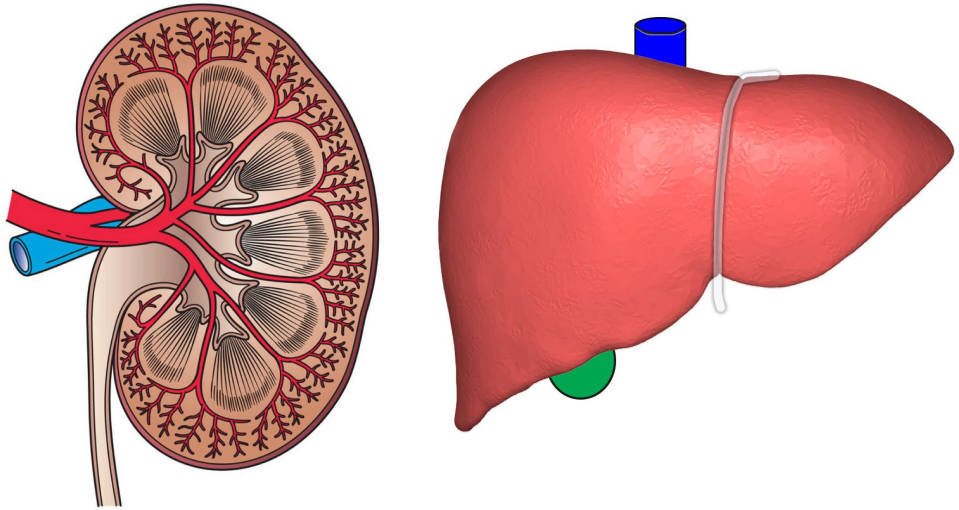
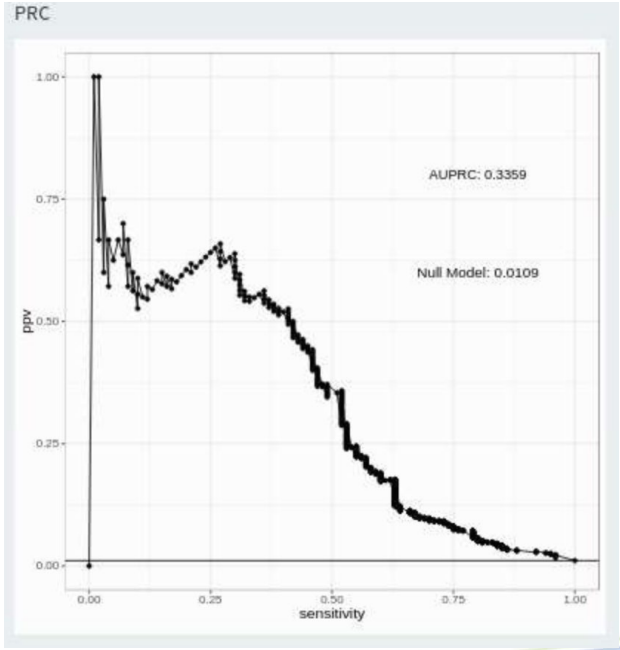
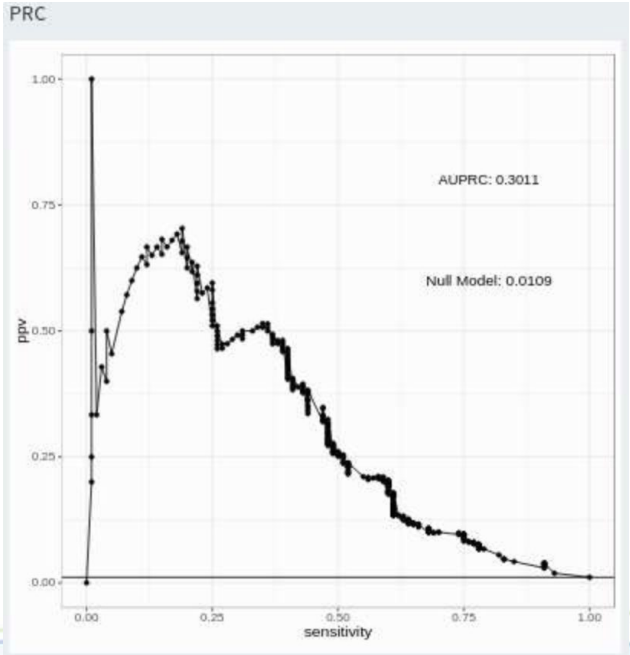
Renal and hepatic dysfunction aren’t important anymore?

- On the contrary! Very important for **management**, **stratification**
- But mortality discrimination equal for 4 vs. 8 organ systems in infected patients, i.e. for **diagnosis** of sepsis they are not necessary







Slide courtesy of SCCM/Bennet/Sanchez-Pinto

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Renal and hepatic dysfunction aren't important anymore?

- **Phoenix-8 score** also developed (in the Supplement) for e.g. research uses

  + Endocrine, Hepatic, Immunologic, and Renal

Internal validation set		
Phoenix-8	PELOD-2	pSOFA
0.91 (0.90-0.91)	0.86 (0.86-0.87)	0.90 (0.89-0.90)
0.90 (0.89-0.91)	0.84 (0.83-0.86)	0.89 (0.87-0.90)
0.85 (0.84-0.86)	0.78 (0.77- 0.79)	0.83 (0.82-0.84)
External validation set		
0.94 (0.94-0.94)	0.92 (0.92-0.92)	0.93 (0.93-0.93)
0.78 (0.76-0.79)	0.70 (0.67-0.71)	0.73 (0.71-0.75)
0.80 (0.79-0.80)	0.73 (0.72-0.74)	0.82 (0.81- 0.83)
0.87 (0.87-0.87)	0.80 (0.80-0.81)	0.86 (0.86-0.87)

Slide courtesy of SCCM/Bennet/Sanchez-Pinto

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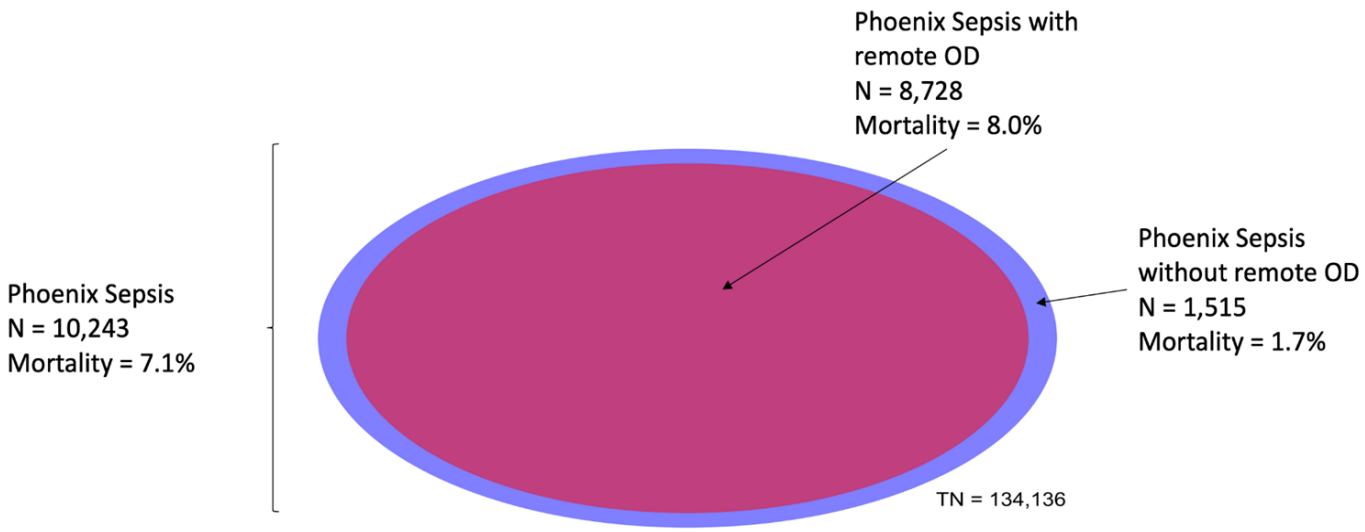
Phoenix-8 score

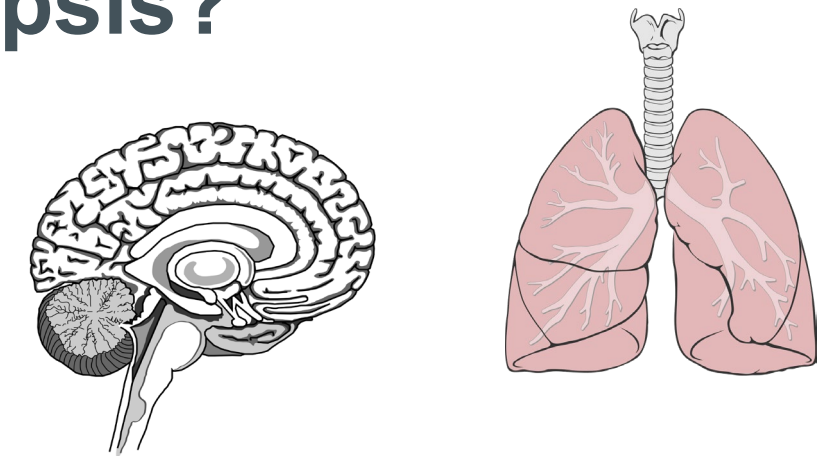
	1 point	2 points	3 points
Respiratory (0-3 points)	P/F <400 or S/F <292	P/F 101-200 and MV or S/F 149-220 and MV	P/F <100 and MV or S/F <148 and MV
Cardiovascular (0-6 points)	1 point each (up to 3 points) for: 1 Vaso-inotrope inf. Lactate 5-10.9 mmol/L MAP (mmHg)	2 points each (up to 6 points) for: ≥2 Vaso-inotrope inf. Lactate ≥11 mmol/L MAP (mmHg)	
Age-based <1 mo. 1-11 mo. 12-23 mo. 24-59 mo. 60-143 mo. 144-216 mo.	 17-30 25-38 31-43 32-44 36-48 38-51	 <17 <25 <31 <32 <36 <38	
Coagulation (0-2 points)	1 point each (max. 2 points) for: Platelets <100 K/µL INR >1.3 D-Dimer >2 mg/L Fibrinogen <100 mg/dL		
Neurologic (0-2 points)	GCS ≤10	Fixed pupils	
Endocrine (0-1 point)	Blood glucose <50 or >150 mg/dL		
Immunologic (0-1 point)	ANC <500 and/or ALC <1000 cells/mm^3		
Renal (0-1 point)			
Age-based <1 mo. 1-11 mo. 12-23 mo. 24-59 mo. 60-143 mo. 144-216 mo.	Creatinine (mg/dL) ≥0.8 ≥0.3 ≥0.4 ≥0.6 ≥0.7 ≥1.0		
Hepatic (0-1 point)	Total bilirubin ≥4mg/dL and/or ALT>102 IU/L		

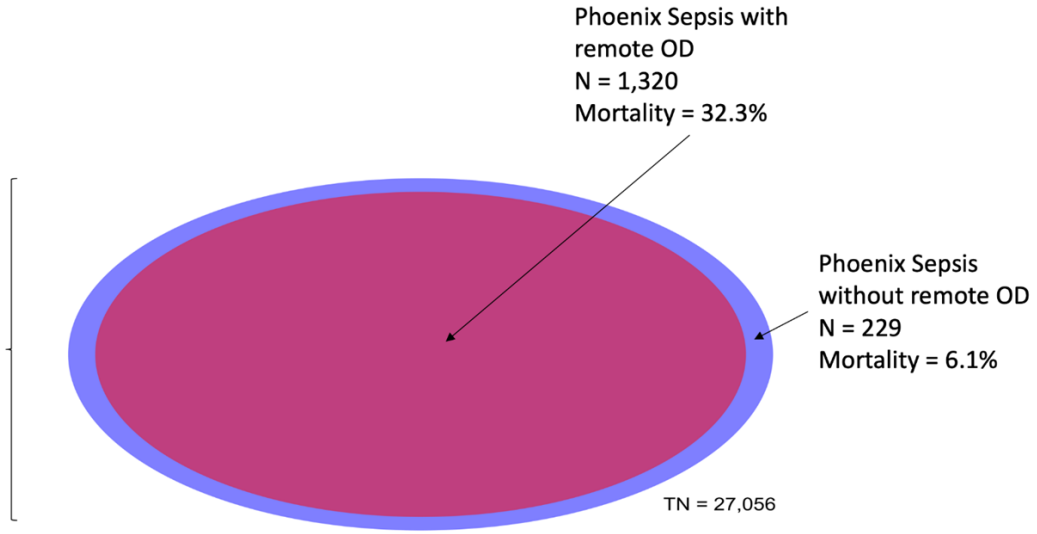
Slide courtesy of SCCM/Bennet/Sanchez-Pinto

Can a child with single-organ respiratory or neurologic dysfunction have sepsis?



Higher Resource Sites





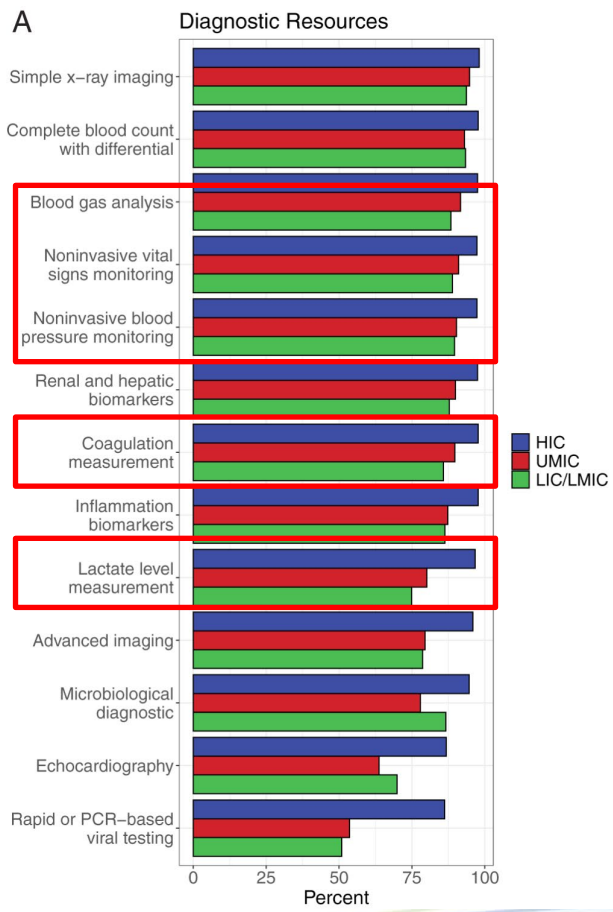
Lower Resource Sites

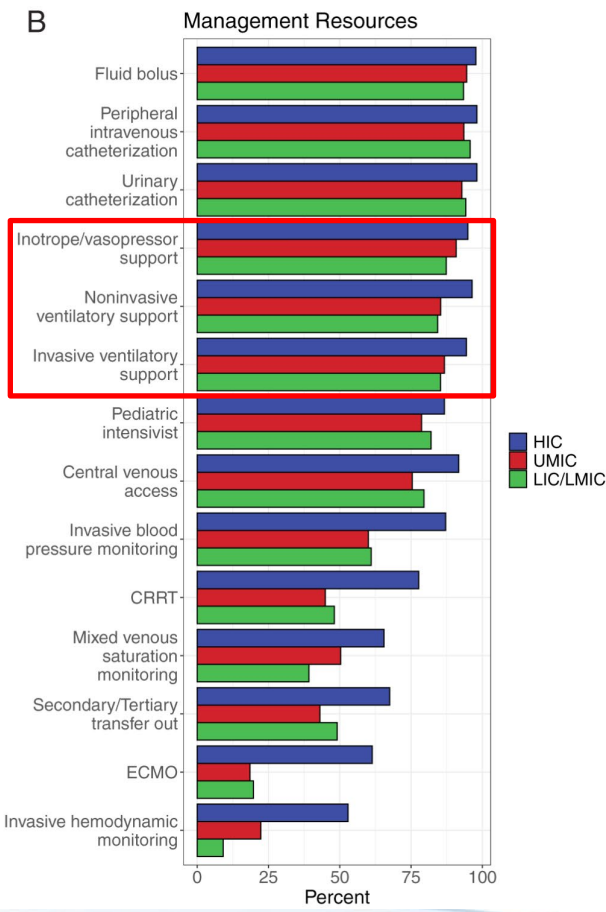
- Yes, but sepsis with “remote” organ dysfunction accounts for the vast majority of cases

Slide courtesy of SCCM/Bennet/Sanchez-Pinto

What if a healthcare facility doesn't routinely collect all variables in the Phoenix Sepsis Score (e.g. D-Dimer)?

- According to **international survey**, most variables in the score are available in most settings
- Score is **built with redundancy**, median score in children with sepsis is 3 (IQR 2 - 4)
- Example: Excellent performance at **lower resource site 1** despite few coagulation tests and lactates





Slide courtesy of SCCM/Bennet/Sanchez-Pinto

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Comparison with Adult Sepsis-3

Similar:

- Sepsis = Infection + organ dysfunction
- Large EHR-based datasets to derive & validate

Different:

- Pediatric dataset was larger, more diverse, more international, and with higher and lower resource sites
- Used AUPRC and PPV/Sensitivity as primary measures instead of AUROC (better approach for imbalanced datasets)
- Used OD subcomponents not entire existing scores (e.g. SOFA)

Slide courtesy of SCCM/Bennet/Sanchez-Pinto

Limitations

- EHR data can have missingness and errors
  - Mitigation: reproducible harmonization and data quality
  - Advantage: Real-world data where criteria will be used
- Some OD is iatrogenic (e.g. GCS in intubated/sedated patients)
- Some lower resource sites had important measures not recorded even when performed (e.g. mechanical ventilation)
- Did not distinguish chronic organ dysfunction (similar to Sepsis-3)
- Data from 2010-2019 from most sites

Slide courtesy of SCCM/Bennet/Sanchez-Pinto

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Tools & resources

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Thank you!

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