Innovations in Data-Driven Approaches to Improve Sepsis Care for Children in Resource-Constrained Settings

Community Risk Stratification and Referral to Higher-level Care

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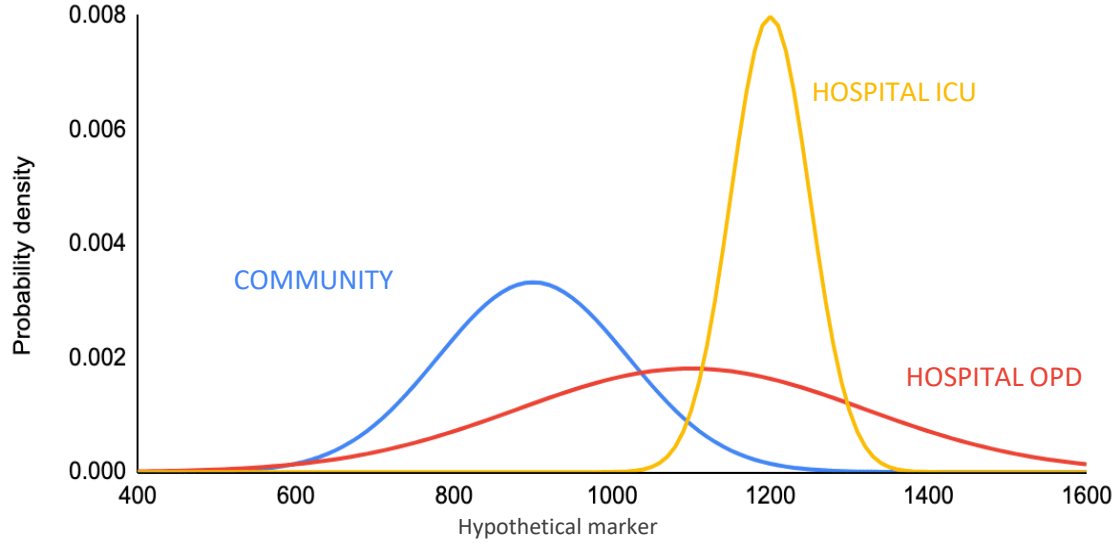
Plan

- Importance of use-cases
- Community assessment of paediatric febrile illness in resource-constrained settings in 2022
- Guiding referral of young children with respiratory infections (the Maela ARI study)
  - Clinical severity scores
  - Biomarkers
- Spot Sepsis trial

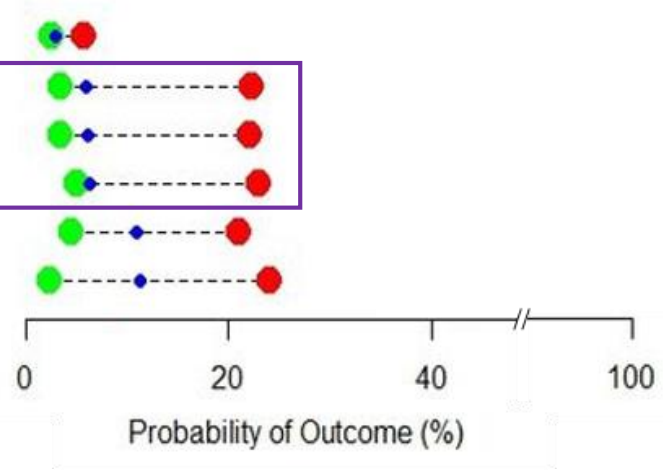
Importance of use-cases

- Differences in case-mix
- Distributions of predictors
- Prevalence of outcomes



- Standardise and contextualise outcomes to understand predictor performance

Study (setting)	Outcome	Prevalence	Cutoff	PLR (95% CI)	NLR (95% CI)
OUTCOME: Mortality, organ dysfunction or PICU admission					
Lactate					
Scott 2017 (USA)	30d mortality	1.9 %	≥ 4mM	2.60 (1.16 - 5.83)	0.87 (0.71 - 1.05)
Mtove 2011 (Tanzania)	In-hospital mortality	5.0 %	> 5mM	5.13 (4.34 - 6.08)	0.49 (0.41 - 0.59)
Nadjm 2013 (Tanzania)	In-hospital mortality	5.1 %	> 5mM	5.00 (4.21 - 5.93)	0.48 (0.40 - 0.58)
Scott 2012 (USA)	Organ dysfunction (24h)	5.4 %	≥ 4mM	4.97 (1.90 - 12.98)	0.74 (0.51 - 1.06)
George 2015 (East Africa)	In-hospital mortality (48h)	9.9 %	> 5mM	2.28 (2.10 - 2.47)	0.34 (0.27 - 0.42)
Aramburo 2018 (East Africa)	In-hospital mortality (72h)	10.3 %	≥ 5mM	2.63 (2.47 - 2.79)	0.13 (0.09 - 0.19)



Chandna et al., BMJ Glob Health, 2021

Importance of use-cases

- Standardise and contextualise outcomes to understand predictor performance

Use-case	Healthcare context	Example resources	Possible outcomes
Community referral	**CHW / VHW** (iCCM)	- **Lay person** - MUAC tapes, thermometers, RR counter - Malaria RDTs - Antipyretics, ACTs, ORS, multivitamins	1. Persistence of symptoms 2. Worsening of symptoms 3. Referral 4. Hospital admission
	PHC / OPD (IMCI or IMAI)	- **Nurse, midwife, clinical officer** - Pulse oximeter, weighing scale, stethoscope - RDTs, basic haematology - Antibiotics, nebulisers, IV fluids	1. Hospital admission 2. Length of stay 3. Critical care admission 4. Organ dysfunction
In-hospital prioritisation	**IPD / ICU** (WHO Pocket Book)	- **Nurse, clinical officer, physician** - Range of clinical equipment - Range of diagnostics - Range of therapeutics	1. Critical care admission 2. Critical care length of stay 3. Organ dysfunction 4. Mortality
Post-discharge follow-up	**IPD**	- **Nurse, clinical officer, physician** - Ability to look at trends during admission - Access to community outreach - Primary care liaison	1. Readmission 2. Return to baseline 3. Neurocognitive outcomes 4. Mortality

BMJ Global Health

Anticipating the future: prognostic tools as a complementary strategy to improve care for patients with febrile illnesses in resource-limited settings

Arjun Chandna [1,2] Jennifer Osborn,[3] Quique Bassat [4,5,6,7,8] David Bell [9] Sakib Burza,[10] Valérie D'Acremont,[11,12] B Leticia Fernandez-Carballo,[3] Kevin C Kain,[13] Mayfong Mayxay,[2,14,15] Matthew Wiens,[16,17,18,19] Sabine Dittrich [2,3]

FIND
Diagnosis for all

ENVIRONMENTAL SCAN

COLAB
For Pediatric Sepsis

wfpiccs.org/pediatric-sepsis-colab

borealisdata.ca/dataverse/EnviroScan_SepsisCoLab

ASSESSMENT

Limited training & supervision
High patient volumes
Lack of diagnostics

REFERRAL

Geographic
Climatic
Security
Political
Financial
Sociocultural

Photos: Liz Ashley, Sakib Burza, Francois Nosten, Frank Smithuis, and Angkor Hospital for Children

Community assessment of paediatric febrile illness in 2022

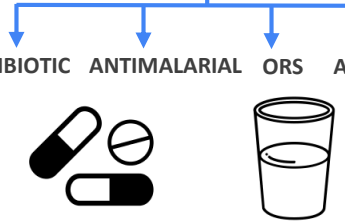
Is this child at risk of progressing to severe illness?

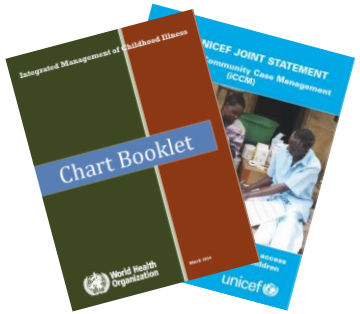
YES | NO

Admit/refer to hospital and/or pre-referral treatment

Community-based treatment

ANTIBIOTIC | ANTIMALARIAL | ORS | ANTIPYRETIC





RESEARCH ARTICLE Open Access

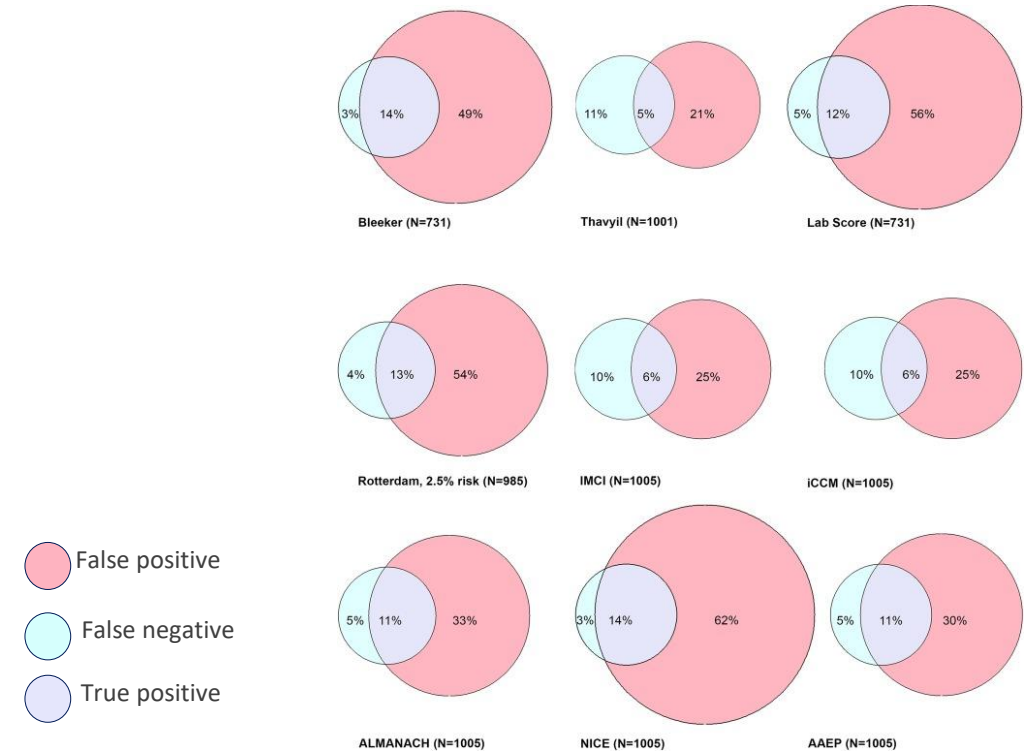
Reliability and validity of pediatric triage tools evaluated in Low resource settings: a systematic review

Bhakti Hansoti[1*], Alexander Jenson[1], Devin Keefe[1], Sarah Stewart De Ramirez[1], Trisha Anest[1], Michelle Twomey[2], Katie Lobner[3], Gabor Kelen[1] and Lee Wallis[2]

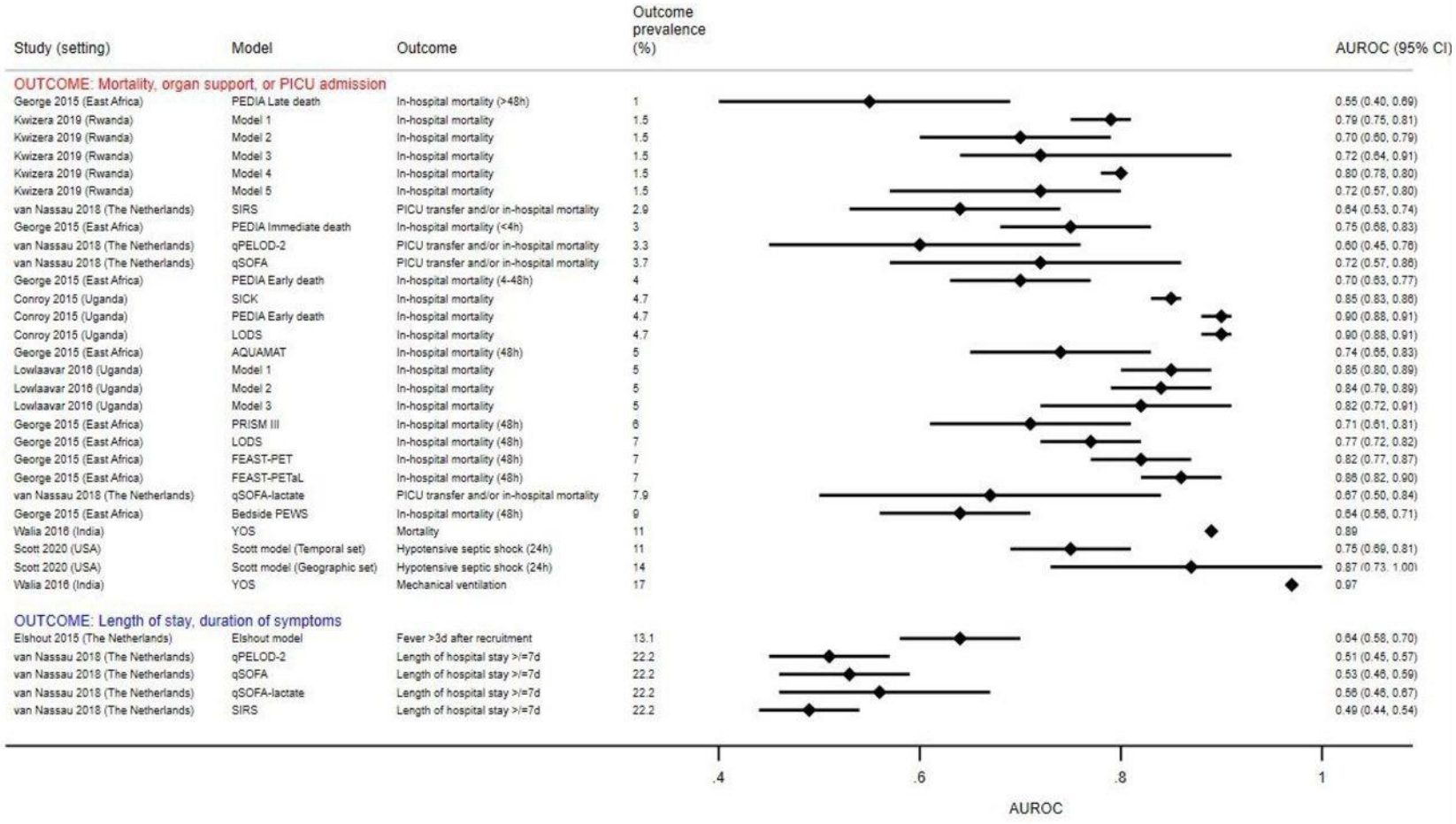
RESEARCH ARTICLE Open Access

Performance of prediction rules and guidelines in detecting serious bacterial infections among Tanzanian febrile children

Kristina Keitel[1,2*], Mary Kilowoko[3], Esther Kyungu[4], Blaise Genton[1,5,6] and Valérie D'Acremont[1,5]



Risk scores / prediction models



Original research

BMJ Global Health

Predictors of disease severity in children presenting from the community with febrile illnesses: a systematic review of prognostic studies

Arjun Chandna ,[1,2] Rainer Tan,[3,4,5] Michael Carter,[6] Ann Van Den Bruel,[7] Jan Verbakel,[7,8] Constantinos Koshiaris,[8] Nahya Salim,[9,10] Yoel Lubell,[2,11] Paul Turner ,[1,2] Kristina Keitel[5,12]

- Few studies
- Hospitalised children
- Infeasible LMIC primary care
- Lack of external validation

Maela ARI study – clinical severity scores

999 pregnant women enrolled
[991 singleton; 8 twin]

965 children born into birth cohort

4,061 acute illness presentations
[810 children]

997 non-ARI presentations

3,064 ARI presentations
[760 children]

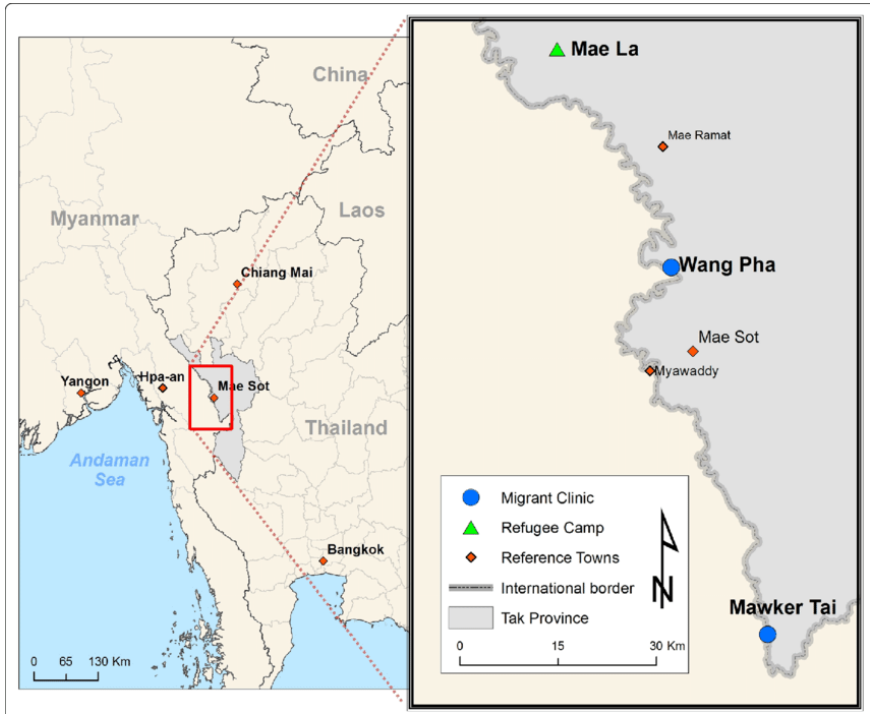
54 ARI presentations with missing outcome status

3,010 ARI presentations included
[756 children]

OPEN ACCESS Freely available online PLOS ONE

High Rates of Pneumonia in Children under Two Years of Age in a South East Asian Refugee Population

Claudia Turner[1,2,3]*, Paul Turner[1,2,3], Verena Carrara[1], Kathy Burgoine[1], Saw Tha Ler Htoo[1], Wanitda Watthanaworawit[1,2], Nicholas P. Day[2,3], Nicholas J. White[2,3], David Goldblatt[4], François Nosten[1,2,3]



- LqSOFA = aRR, aHR, CRT, AVPU
- mSIRS = aRR, aHR, temperature
- qPELOD-2 = HR, CRT, AVPU
- Externally validate and update
- Primary outcome: supplemental oxygen (SpO_2 < 90%)

Romaine et al., Pediatrics, 2020; Beane et al., J Acute Med, 2017; Leclerc et al., Ped Crit Care Med, 2017

Maela ARI study – clinical severity scores

Baseline Characteristics	Overall N = 3,010	Supplemental oxygen	
		No N = 2,906	Yes N = 104
Age (months)	8.1 (3.7, 13.7)	8.2 (3.8, 13.8)	7.3 (3.4, 12.7)
Male sex	53% (1,592 / 3,010)	53% (1,541 / 2,906)	49% (51 / 104)
Gestation (weeks)	39.1 (38.1, 40.0)	39.2 (38.2, 40.0)	38.4 (37.3, 39.7)
Birthweight (kg)	2.9 (2.6, 3.2)	2.9 (2.6, 3.2)	2.6 (2.0, 3.0)
Symptom duration (days)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)
Fever	65% (1,958 / 3,005)	65% (1,885 / 2,901)	70% (73 / 104)
Cough	92% (2,767 / 3,010)	92% (2,667 / 2,906)	96% (100 / 104)
● Respiratory distress*	17% (508 / 3,009)	**14%** (416 / 2,905)	**88%** (92 / 104)
Lung crepitations	39% (1,158 / 2,941)	38% (1,085 / 2,844)	75% (73 / 97)
● Heart rate (bpm)			
Neonate	140 (132, 150)	**140** (132, 148)	**150** (140, 165)
Infant	138 (128, 144)	**136** (128, 144)	**147** (137, 154)
Child	128 (120, 140)	**128** (120, 140)	**140** (128, 149)
● Respiratory rate (bpm)			
Neonate	48 (45, 56)	**48** (44, 54)	**65** (54, 77)
Infant	48 (42, 56)	**48** (42, 56)	**58** (54, 66)
Child	45 (38, 52)	**44** (38, 52)	**57** (47, 62)
● Axillary temperature (°C)	36.6 (36.0, 37.5)	**36.6** (36.0, 37.4)	**36.8** (36.2, 37.8)
● Capillary refill time > 2 secs	1.4% (36 / 2,568)	**1.1%** (27 / 2,476)	**9.8%** (9 / 92)
● Not alert	13% (372 / 2,973)	**11%** (306 / 2,875)	**67%** (66 / 98)
● Weight-for-age z-score (WAZ)	-0.9 (-1.6, -0.2)	**-0.9** (-1.6, -0.2)	**-1.9** (-3.4, -0.8)

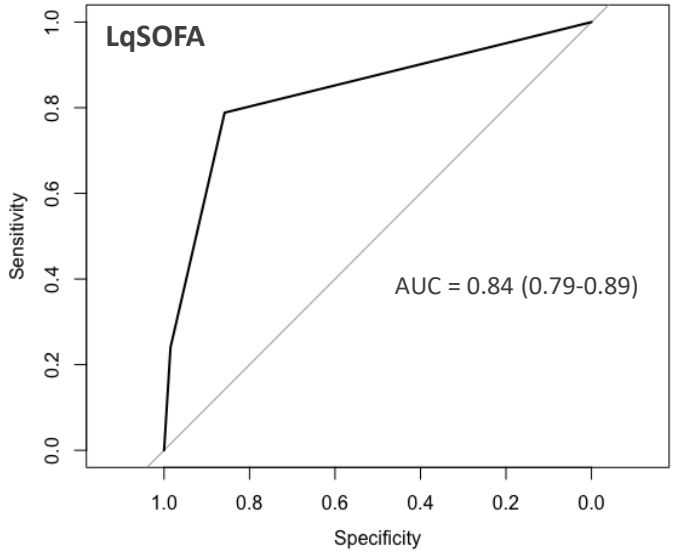
● Variable part of clinical score(s)

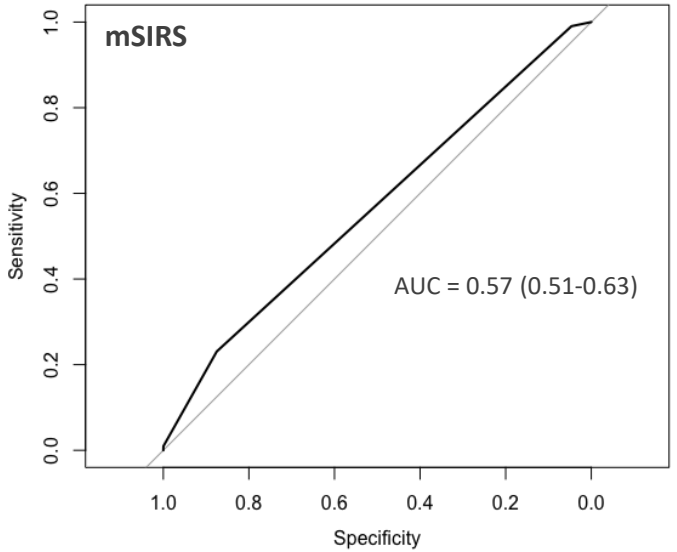
*Respiratory distress = head bobbing, grunting, nasal flaring, tracheal tug and/or chest indrawing

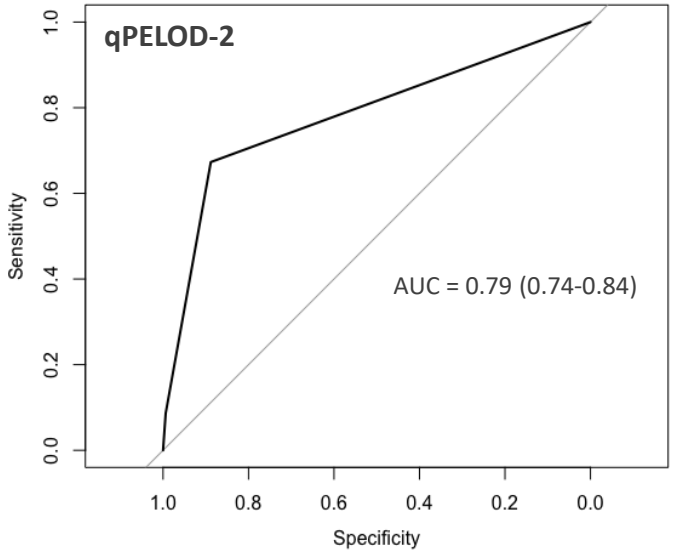
Median (IQR) reported for continuous variables

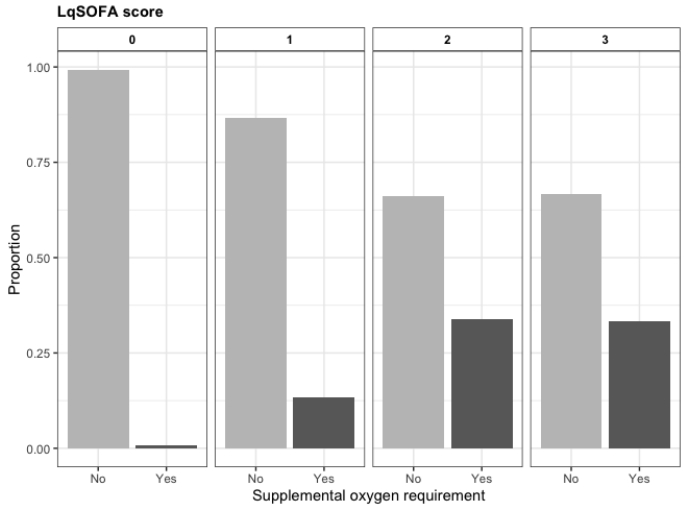
Maela ARI study – clinical severity scores

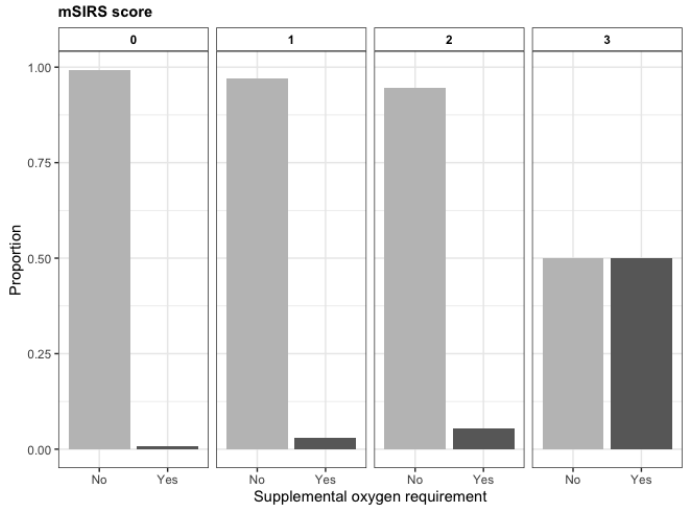
External validation of the existing scores

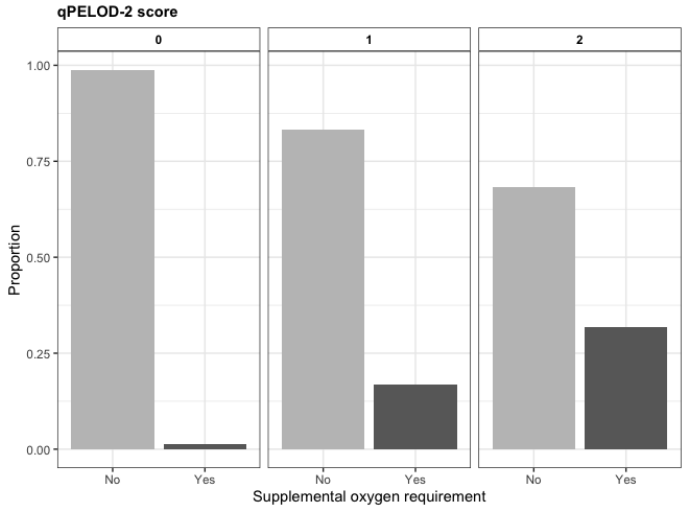






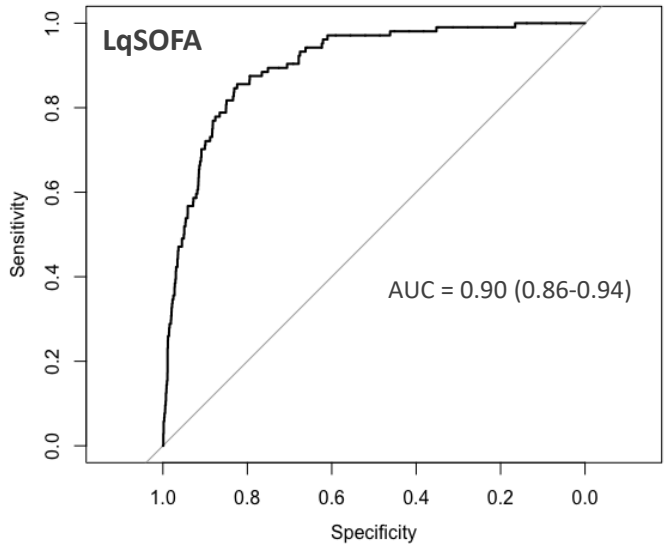


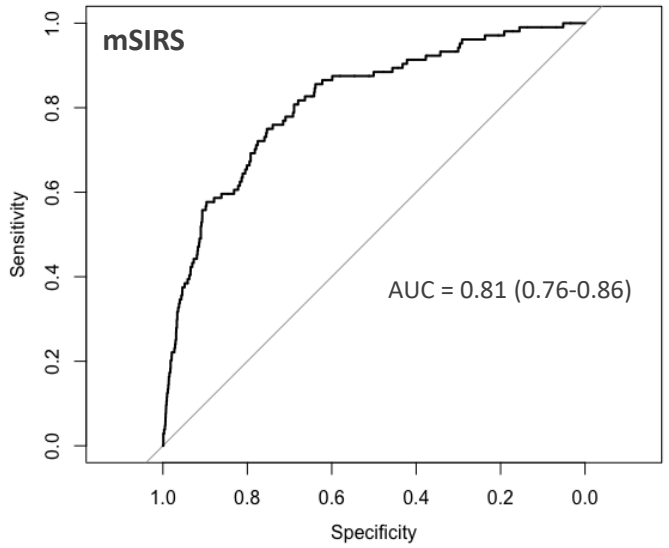


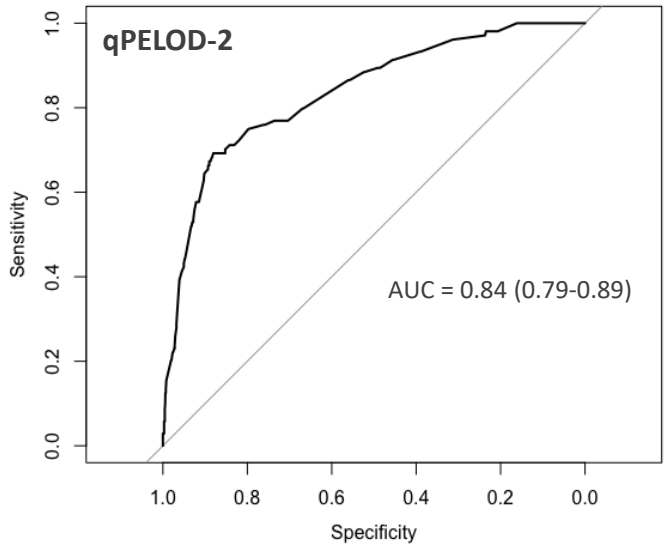


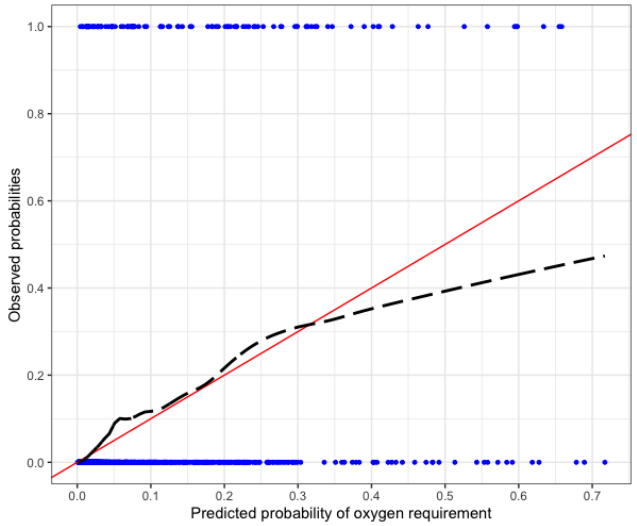
Maela ARI study – clinical severity scores

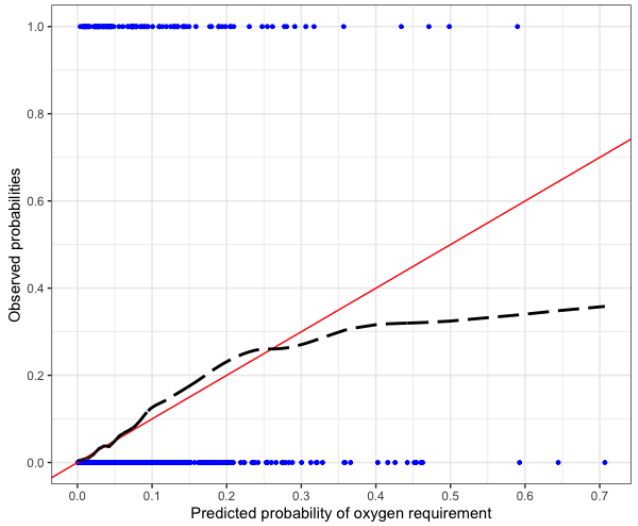
Conversion to prediction models

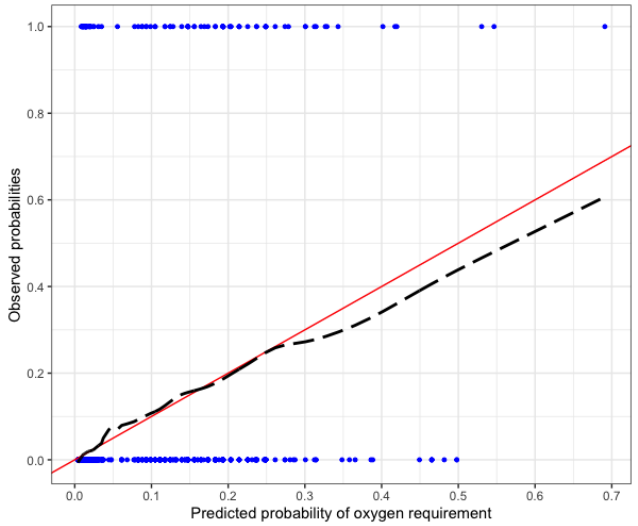






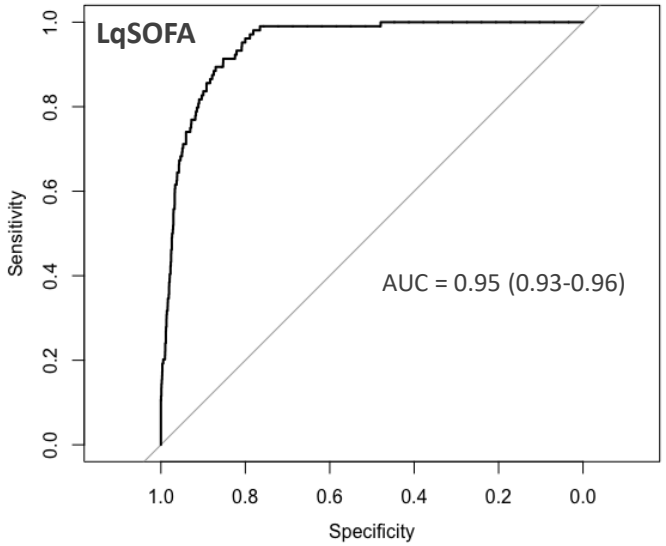


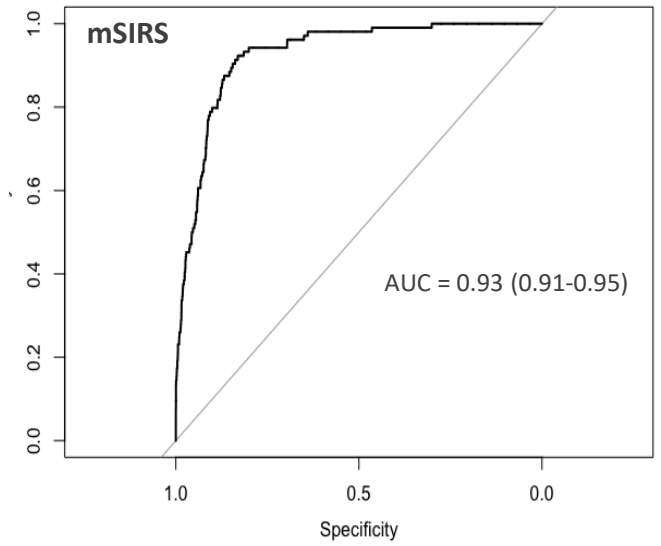


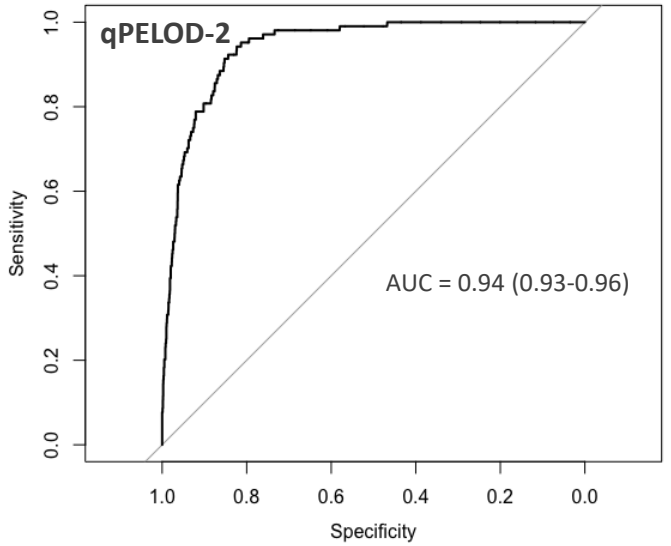


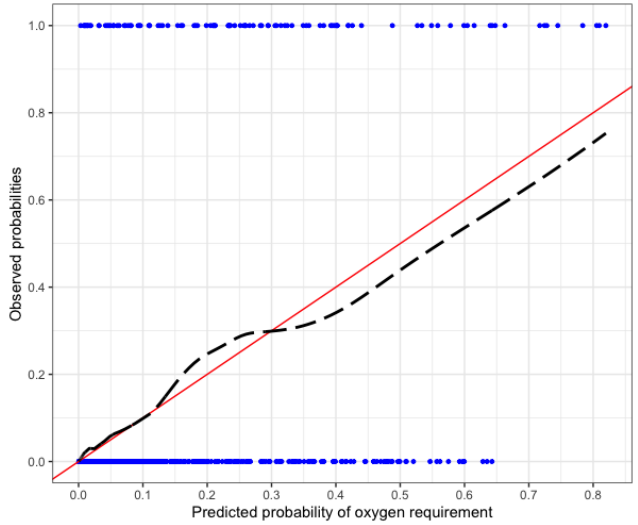
Maela ARI study – clinical severity scores

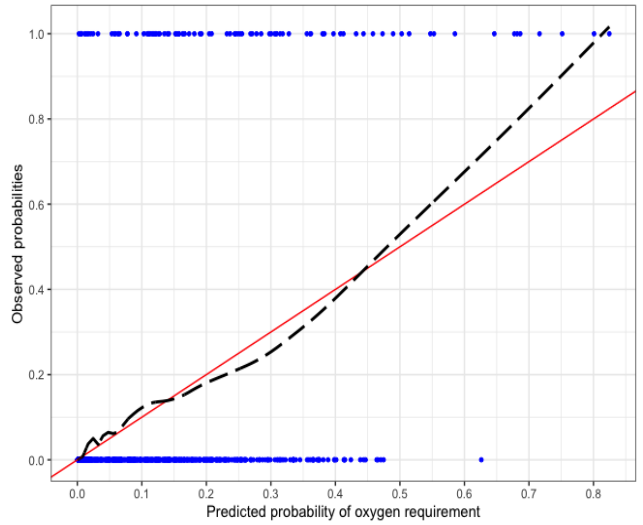
Updated models (addition of WAZ and respiratory distress)

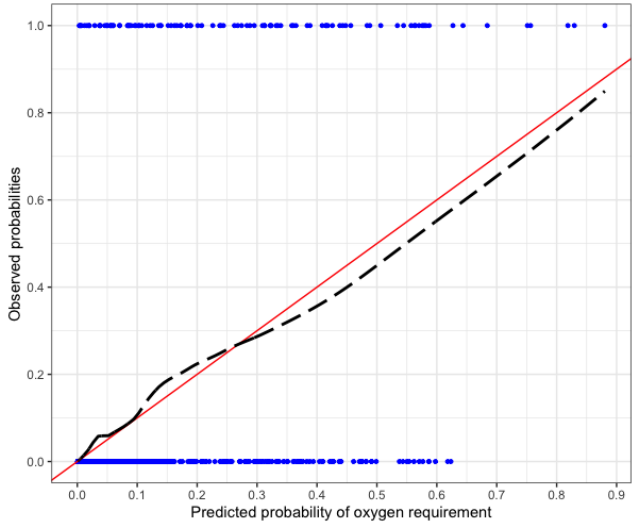






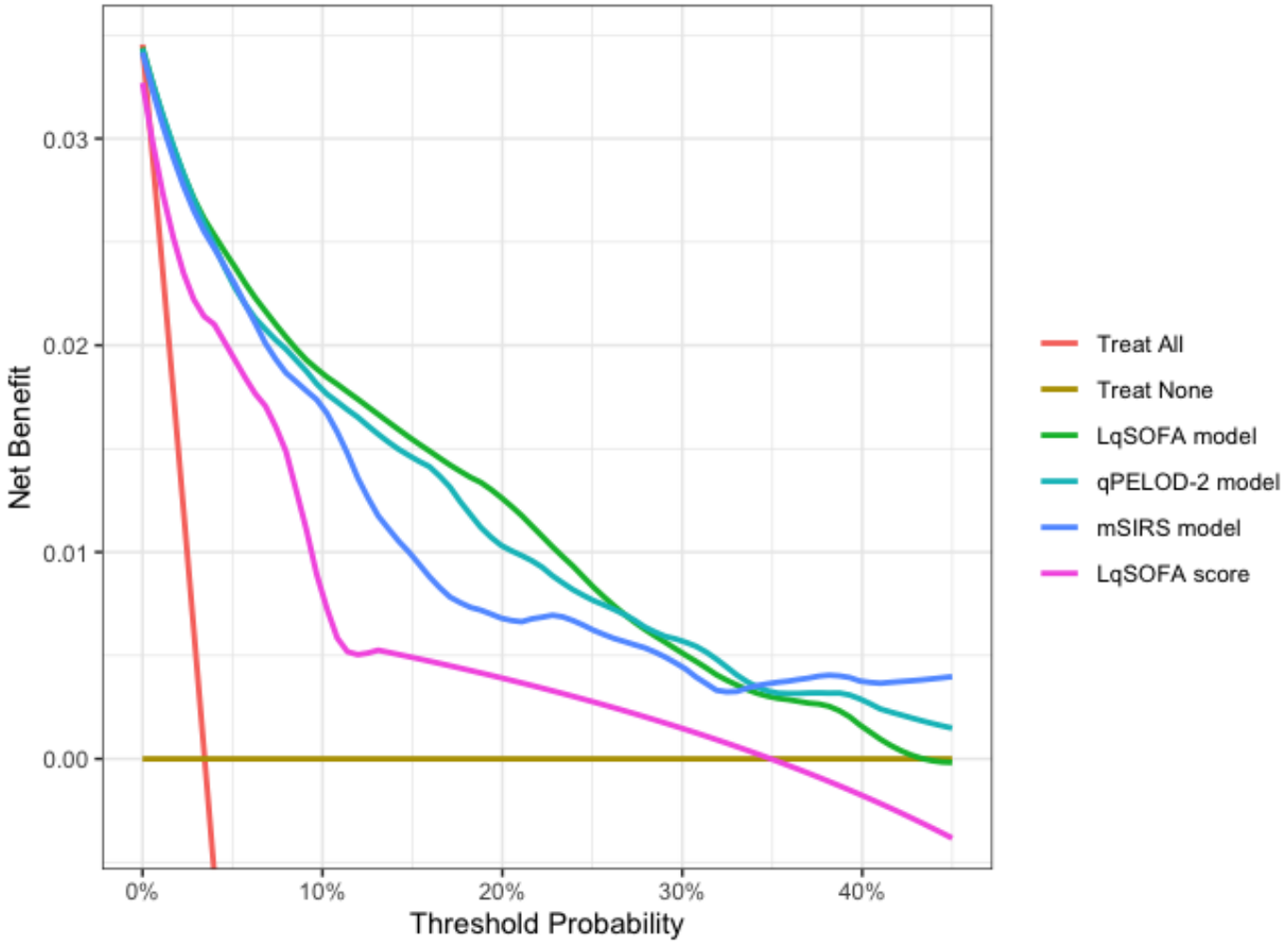






Maela ARI study – clinical severity scores

Decision curves – referral decisions based on **the models** vs. **LqSOFA score** vs. **refer all** vs. **refer none**



Threshold probability of 5% = one correct referral is valued as much as 19 incorrect referrals (1 TP ≈ 19 FP)

Threshold probability of 20% = one correct referral is valued as much as 4 incorrect referrals (1 TP ≈ 4 FP)

Maela ARI study – clinical severity scores

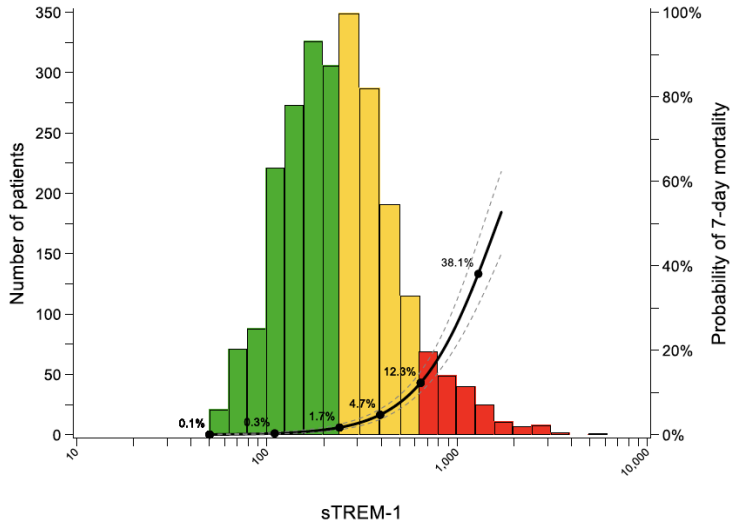
Referral threshold	Sensitivity	Specificity	Negative Likelihood Ratio	Positive Likelihood Ratio	Cases referred (%)	Cases managed in community (%)	Ratio of Incorrect to Correct referrals	Ratio of Correct to Incorrect cases managed in community
LqSOFA model								
5%	0.86	0.89	0.16	7.45	423 (14.1%)	2587 (85.9%)	4 to 1	171 to 1
10%	0.74	0.93	0.28	11.15	270 (9.0%)	2740 (91.0%)	3 to 1	100 to 1
20%	0.61	0.97	0.41	17.96	161 (5.3%)	2849 (94.7%)	2 to 1	68 to 1
LqSOFA score								
≥ **1**	0.80	0.86	0.23	5.89	407 (16.1%)	2118 (83.9%)	5 to 1	131 to 1
≥ **2**	0.23	0.98	0.78	15.49	68 (2.7%)	2457 (97.3%)	3 to 1	39 to 1
≥ **3**	0.01	1.00	0.99	15.09	1 (< 0.01%)	2524 (> 99.9%)	0 to 1	31 to 1

Maela ARI study – biomarkers

nature COMMUNICATIONS

Risk-stratification of febrile African children at risk of sepsis using sTREM-1 as basis for a rapid triage test

Aleksandra Leligdowicz[1], Andrea L. Conroy[2], Michael Hawkes[3], Melissa Richard-Greenblatt[4], Kathleen Zhong[4], Robert O. Opoka[5], Sophie Namasopo[6], David Bell[7], W. Conrad Liles[8], Bruno R. da Costa[9], Peter Jüni[9,11] & Kevin C. Kain[10,11]✉



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association

Prognostic Accuracy of Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM-1)-based Algorithms in Febrile Adults Presenting to Tanzanian Outpatient Clinics

Melissa Richard-Greenblatt,[1,2] Noémie Boillat-Blanco,[2] Kathleen Zhong,[1] Zainab Mbarack,[3] Josephine Samaka,[4] Tarsis Mlaganile,[4] Thekla Kazimoto,[4] Valerie D'Acremont,[5,6] and Kevin C. Kain[7]

RESEARCH ARTICLE Open Access

sTREM-1 predicts mortality in hospitalized patients with infection in a tropical, middle-income country

Shelton W. Wright[1], Lara Lovelace-Macon[2], Viriya Hantrakun[3], Kristina E. Rudd[4], Prapit Teparrukkul[5], Susanna Kosamo[2], W. Conrad Liles[6], Direk Limmathurotsakul[3,7] and T. Eoin West[2,8*]

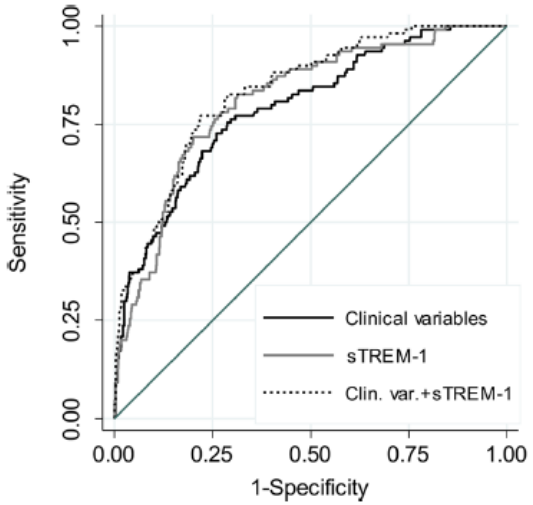


Table 4 Discrimination of mortality by LASSO-selected biomarkers

Model	AUC	95% CI	*p* value[a]
IL-8+Ang-2+sTREM-1	0.83	0.79–0.87	Ref
IL-8	0.77	0.73–0.81	0.002
Ang-2	0.77	0.73–0.82	0.0002
sTREM-1	0.81	0.77–0.85	0.07

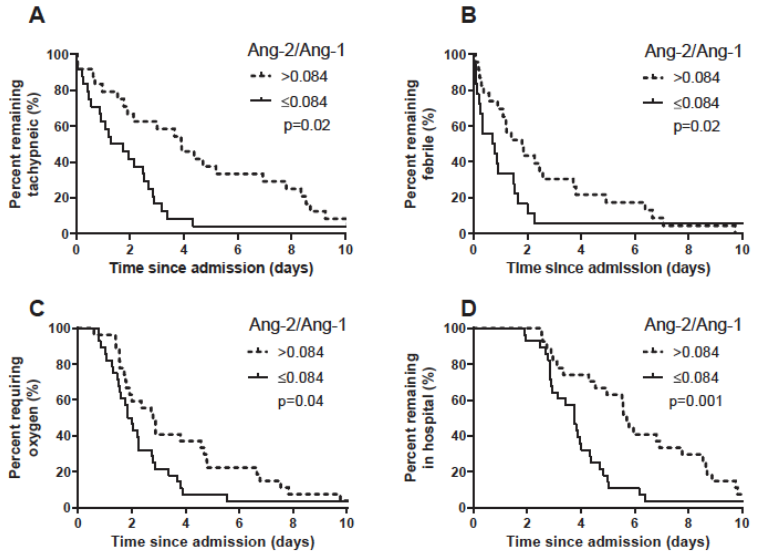
ELSEVIER

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Dysregulation of angiopoietin-Tie-2 axis in ugandan children hospitalized with pneumonia

Ran Zhang[a], Urvi Rai[a], Nafeesah Bte Mohamed Ibrahim[a], Yanni Amazouz[a], Jeremy Soo[a], Andrea L. Conroy[b], Sophie Namasopo[c,1], Robert O. Opoka[d], Ravi Bhargava[e], Michael T. Hawkes[f,g,h,i,j,*]

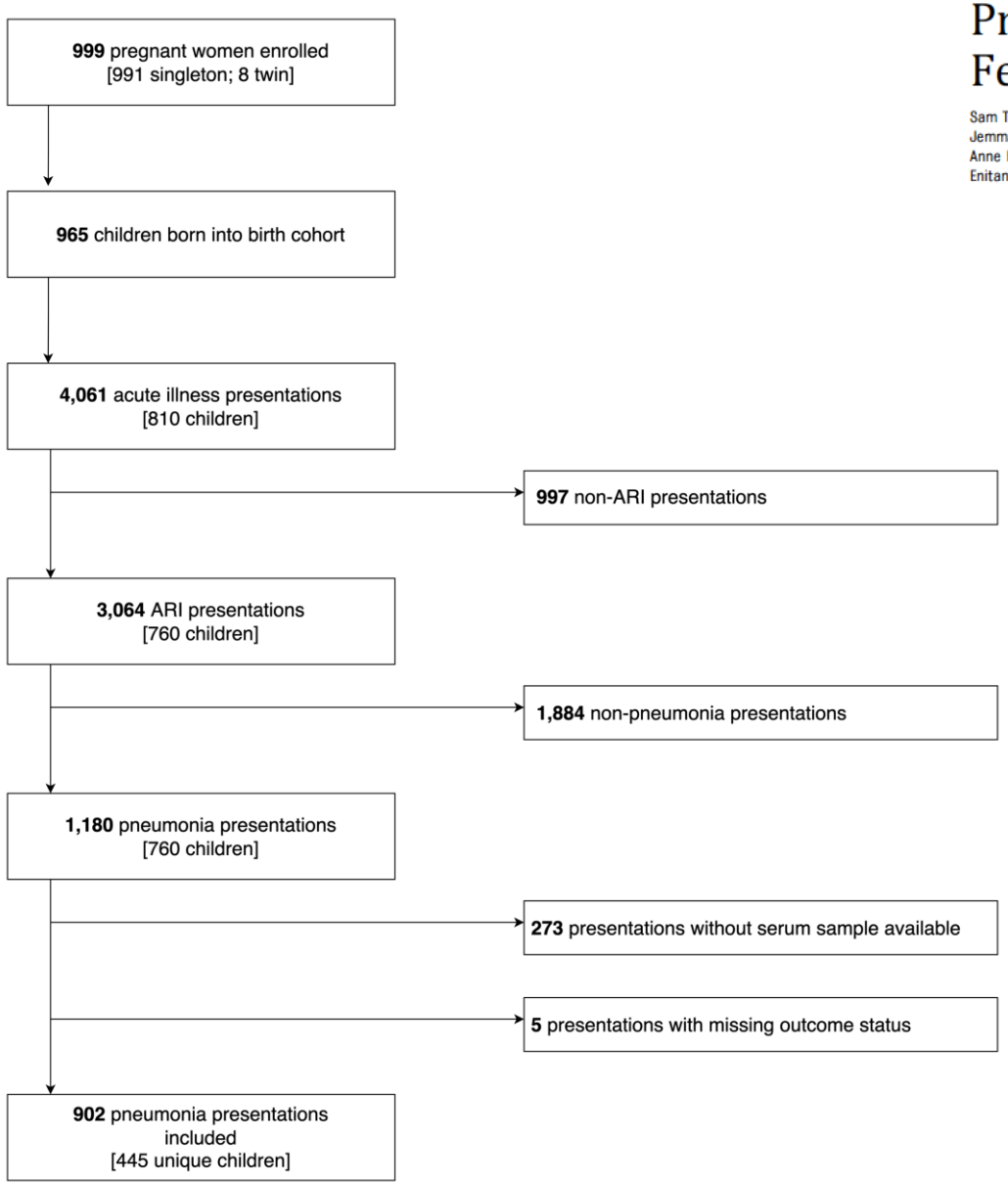


Pediatric Cardiology

Endothelial Dysfunction in Childhood Infection

Marietta Charakida, MD; Ann E. Donald, AVS; Mari Terese, BSc (Hons), AVS; Sam Leary, PhD; Julian P. Halcox, MB, MA, MRCP; Andy Ness, PhD, MFPH; George Davey Smith, MD, DSc, FFPH; Jean Golding, PhD, DSc, FMedSci; Peter Friberg, MD, PhD; Nigel J. Klein, PhD, FRCPCH; John E. Deanfield, BA, BCh, MB, FRCP; for the ALSPAC (Avon Longitudinal Study of Parents and Children) Study Team

Maela ARI study – biomarkers



PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Accuracy of a Modified qSOFA Score for Predicting Critical Care Admission in Febrile Children

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scientific reports
OPEN

Age-adjusted quick Sequential Organ Failure Assessment score for predicting mortality and disease severity in children with infection: a systematic review and meta-analysis

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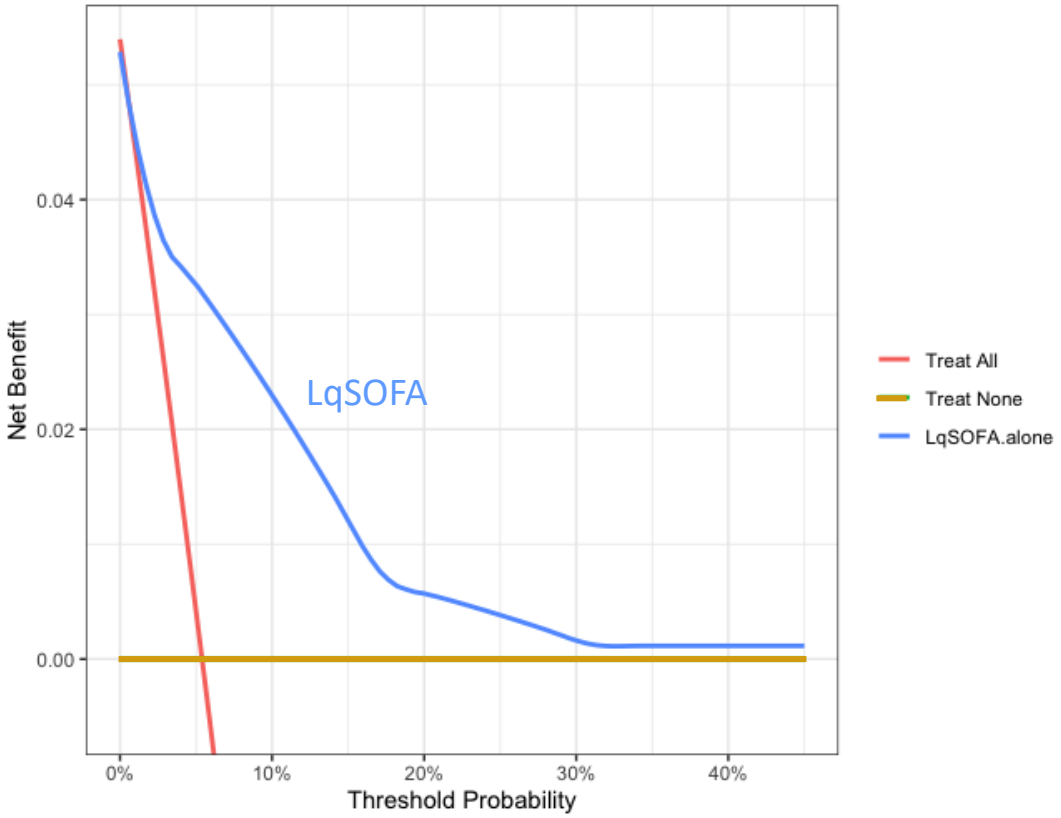
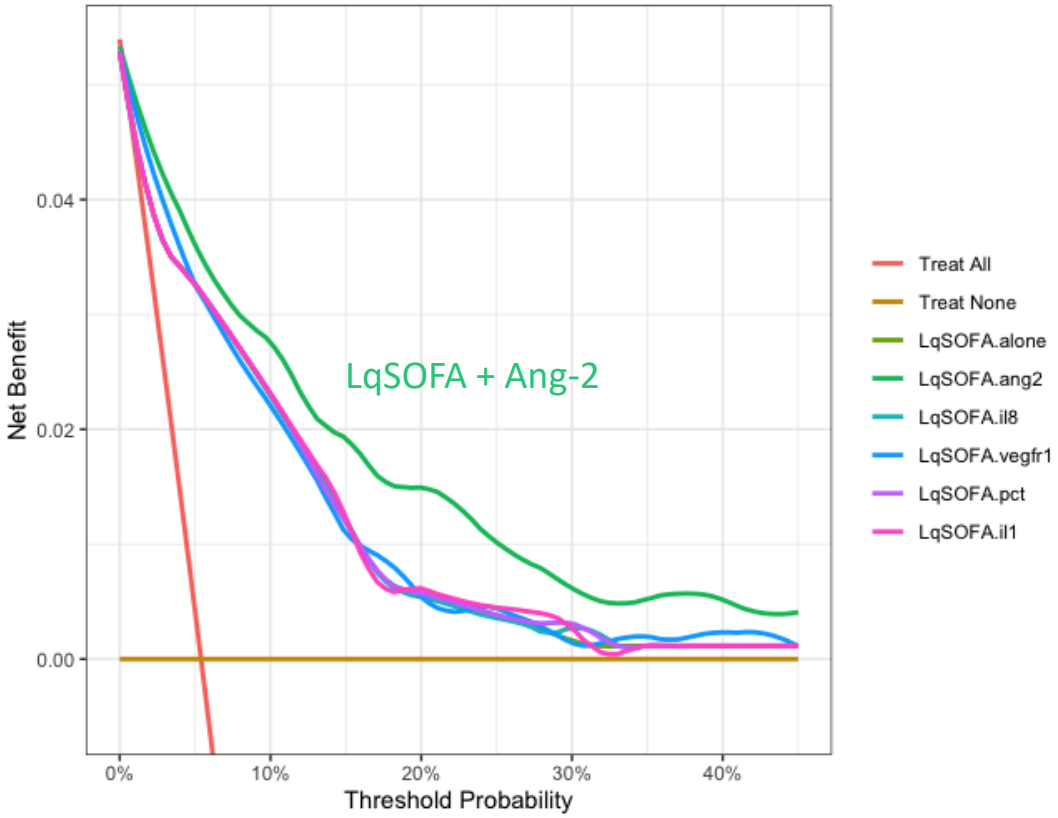
- LqSOFA = aRR, aHR, CRT, AVPU
- Evaluate predictive performance of biomarkers
  - Generate data to guide prospective research
  - Explore diagnosis vs. prognosis
- Supplemental oxygen (SpO_2 < 90%)
- 49/902 (5.4%) met endpoint

Maela ARI study – biomarkers

Biomarker	AUC (95% CI)	
	Univariate	+ LqSOFA
LqSOFA	0.82 (0.76-0.88)	–
Ang-2	0.81 (0.74-0.87)	0.91 (0.88-0.94)
IL-8	0.72 (0.65-0.79)	0.89 (0.85-0.92)
sVEGFR-1	0.70 (0.62-0.78)	0.89 (0.86-0.93)
PCT	0.69 (0.62-0.77)	0.79 (0.70-0.87)
IL-1	0.68 (0.59-0.77)	0.80 (0.72-0.88)
IL-6	0.65 (0.56-0.73)	
sTNFR-1	0.64 (0.55-0.72)	
IL-10	0.61 (0.53-0.70)	
CXCL-10 / IP-10	0.58 (0.49-0.66)	
sTREM-1	0.56 (0.49-0.63)	
CRP	0.56 (0.47-0.65)	
Ang-1	0.53 (0.44-0.62)	
CHI3L1	0.51 (0.42-0.60)	

Maela ARI study – biomarkers



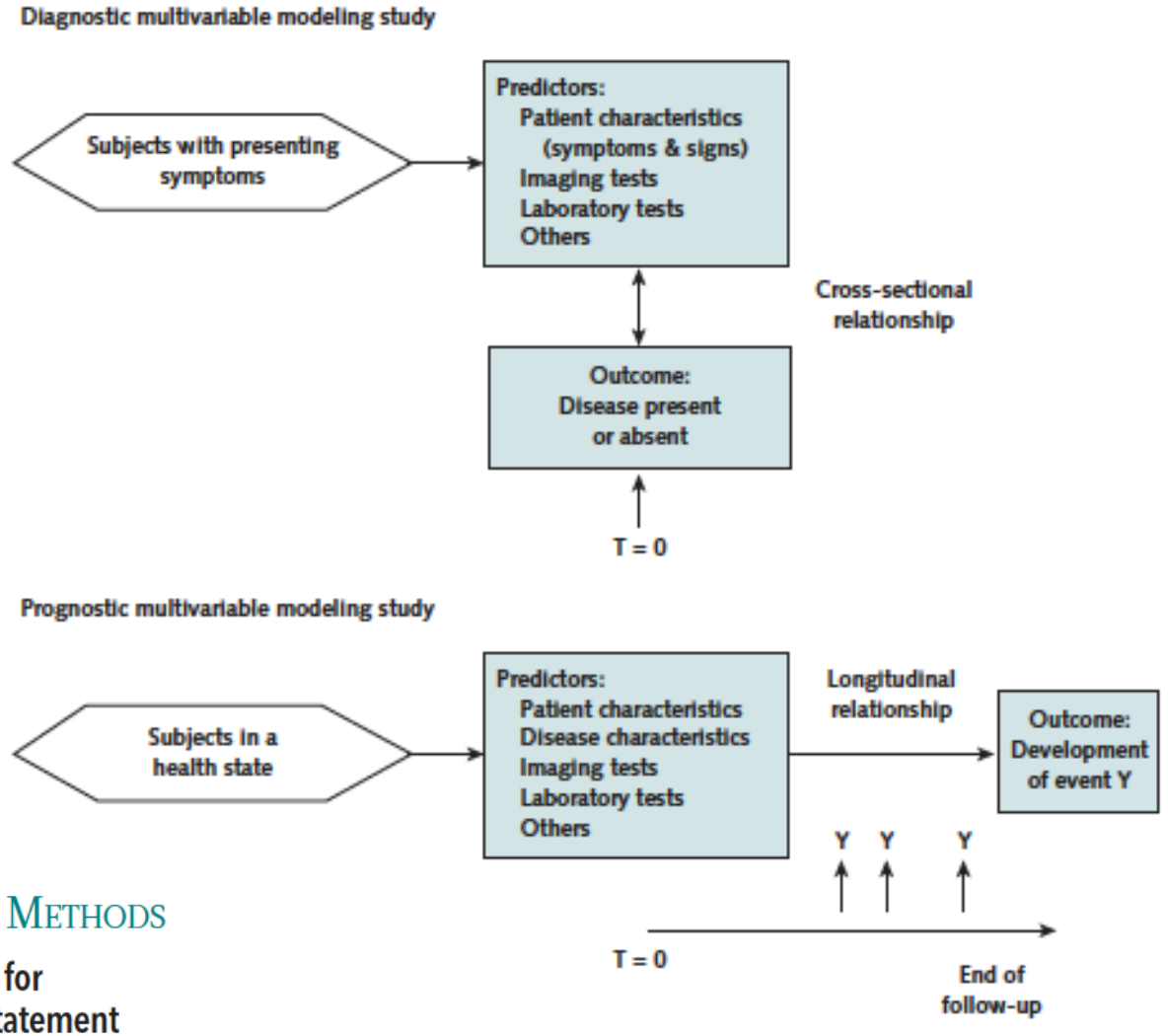


Maela ARI study – biomarkers

Referral threshold	Sensitivity	Specificity	Negative Likelihood Ratio	Positive Likelihood Ratio	Cases referred (%)	Cases managed in community (%)	Ratio of Incorrect to Correct referrals	Ratio of Correct to Incorrect cases managed in community
LqSOFA score								
1% (~ ≥ 0)	1.00	0.00	1.00	1.00	871 (100.0%)	0 (0.0%)	18 to 1	–
5% (~ ≥ 1)	0.77	0.83	0.28	4.38	176 (20.2%)	695 (80.0%)	4 to 1	62 to 1
20% (~ ≥ 2)	0.21	0.98	0.81	8.77	26 (3.0%)	845 (97.0%)	2 to 1	22 to 1
40% (~ ≥ 3)	0.02	1.00	0.98	1.00	1 (0.1%)	870 (99.9%)	0 to 1	18 to 1
LqSOFA + Ang-2								
1%	1.00	0.36	0.00	1.57	574 (65.9%)	297 (34.1%)	11 to 1	Inf to 1
5%	0.85	0.81	0.18	4.38	197 (22.6%)	674 (77.4%)	4 to 1	95 to 1
20%	0.45	0.96	0.58	11.51	54 (6.2%)	817 (93.8%)	2 to 1	30 to 1
40%	0.23	0.99	0.77	21.43	19 (2.2%)	852 (97.8%)	1 to 1	23 to 1

Language of prediction

Figure 1. Schematic representation of diagnostic and prognostic prediction modeling studies.



Annals of Internal Medicine RESEARCH AND REPORTING METHODS

Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD Statement

Gary S. Collins, PhD; Johannes B. Reitsma, MD, PhD; Douglas G. Altman, DSc; and Karel G.M. Moons, PhD

Maela ARI study – biomarkers

DIAGNOSTIC → **PROGNOSTIC**

Outcome A	
Biomarker	**AUC** (95% CI)
LqSOFA	0.82 (0.76-0.88)
Ang-2	0.81 (0.74-0.87)
IL-8	0.72 (0.65-0.79)
sVEGFR-1	0.70 (0.62-0.78)
PCT	0.69 (0.62-0.77)
IL-1	0.68 (0.59-0.77)

Outcome 1	
Biomarker	**AUC** (95% CI)
LqSOFA	0.85 (0.78-0.91)
Ang-2	0.74 (0.65-0.84)
sVEGFR-1	0.71 (0.62-0.81)
IL-1	0.71 (0.61-0.81)
IL-8	0.70 (0.62-0.77)
PCT	0.69 (0.59-0.78)

Outcome 2	
Biomarker	**AUC** (95% CI)
Ang-2	0.80 (0.70-0.90)
IL-8	0.75 (0.64-0.85)
LqSOFA	0.75 (0.64-0.85)
PCT	0.68 (0.56-0.80)
IL-1	0.66 (0.53-0.79)
sVEGFR-1	0.63 (0.51-0.75)

Outcome 3	
Biomarker	**AUC** (95% CI)
IL-8	0.75 (0.68-0.82)
Ang-2	0.72 (0.64-0.81)
IL-1	0.71 (0.62-0.80)
sVEGFR-1	0.67 (0.58-0.76)
PCT	0.67 (0.58-0.75)
LqSOFA	0.65 (0.57-0.73)

Outcomes

A = Supplemental oxygen during acute illness (853 controls; 49 cases)

1 = SpO_2 < 90% at presentation (735 controls; 32 cases)

2 = Supplemental oxygen during acute illness, excluding those with SpO_2 < 90% at presentation (848 controls; 23 cases)

3 = Supplemental oxygen within next 28 days, excluding those with SpO_2 < 90% at presentation (826 controls; 39 cases)

Spot Sepsis

Study sites

BANGLADESH – Cox Bazar

CAMBODIA – Siem Reap

INDONESIA – Yogyakarta

LAOS – Salavan, Savannakhet

VIET NAM – Dong Nai, Hanoi

Partners

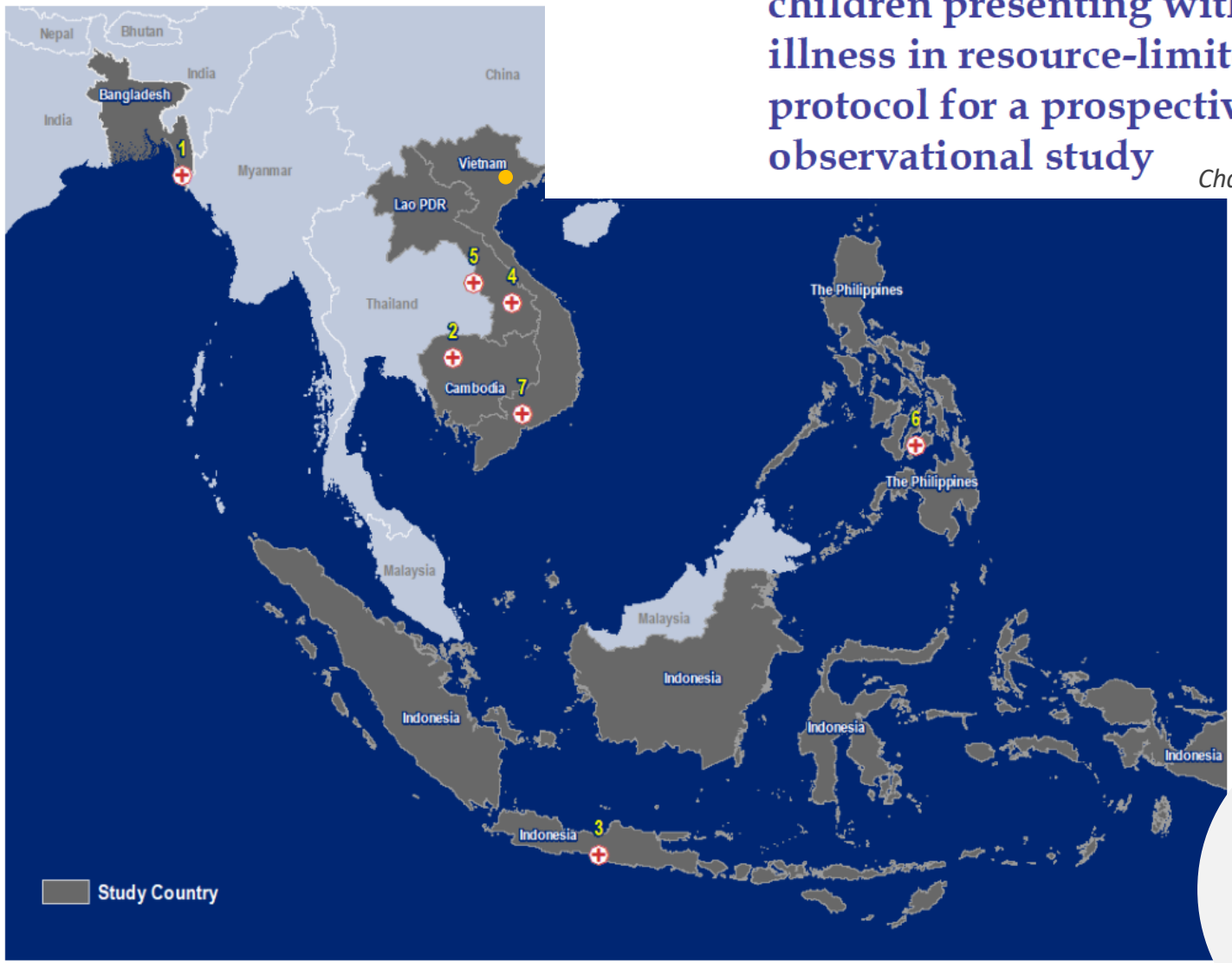
Funders

Open access Protocol

BMJ Open

Prediction of disease severity in young children presenting with acute febrile illness in resource-limited settings: a protocol for a prospective observational study

Chandna et al., BMJ Open, 2021



3,336 participants recruited to date

Take-aways

- **Reliability and validity** of current tools to guide referral from primary to secondary care is **poor**
- **Standardisation** of (non-mortality) outcomes and **contextualisation** (of all) **outcomes** could help data sharing and comparisons across studies
- **LqSOFA** looks like a **promising** and **practical** paediatric version of qSOFA
- **Biomarkers** should be assessed by the **value they add** to clinical scores

Useful documents

- TRIPOD guidelines

https://www.equator-network.org/reporting-guidelines/tripod-statement/

- Collection of materials on best practices for prognostic research

https://www.prognosisresearch.com/

- Environmental scan to assess level of care

https://borealisdata.ca/dataverse/EnviroScan_SepsisCoLab

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- Team **COMRU**
- **You** for listening :)

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