Endothelial Dysfunction Criteria in Critically Ill Children:

The PODIUM Consensus Conference

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Data Supplement

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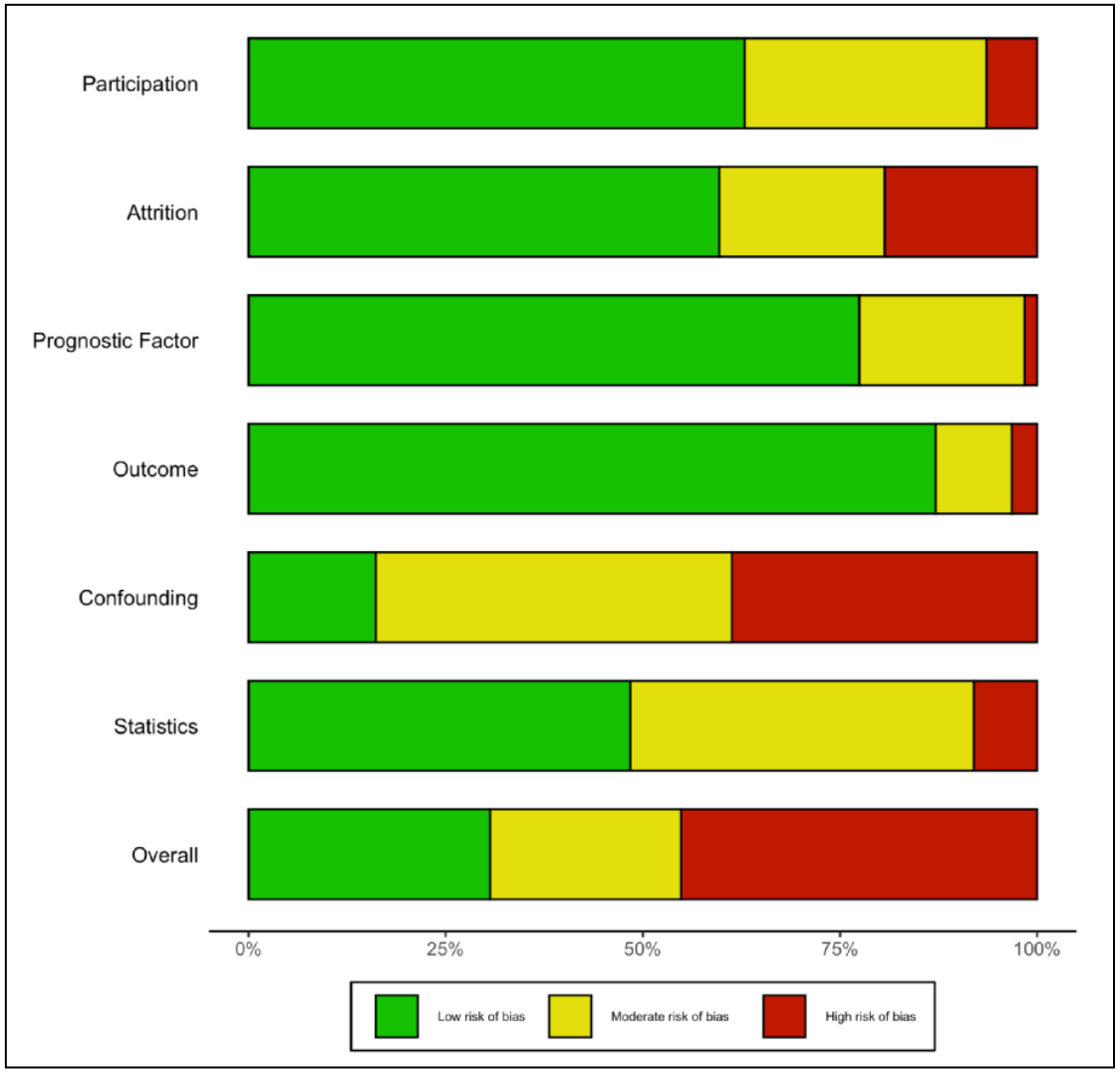

Supplemental Table 1. Studies Included in the PODIUM Endothelial Dysfunction Systematic Review (n=62 studies)

Author (yr)	Funding	Study design	Location	No. of sites	Study years	Setting	Data source(s)	Sample size	Recruitment	Age categories[a]	Age details[b]
Abo-Hagar (2017)	Other (No financial support)	Prospective cohort	Egypt	1	2014-2015	PICU of unknown composition	Prospective data collection	35	NR/Unable to determine	Infants Children Adolescents	Patients: 5.05 (3.51) and control 5.56 (3.79) yr
Al Yaman (1996)	Govt. NGO	Observational/ descriptive study	Papua New Guinea	1	1991-1994	NR/Unable to determine	Prospective data collection	92	Convenience	Children	Mean 4.2 yr (2.1)
Al-Bitalgi (2017)	Other (Self)	Prospective cohort	Egypt	1	2012-2013	PICU of unknown composition	Chart review Prospective data collection	40	Convenience	Infants Children	Mean 23.7 (21.6) mo
Apltz (2012)	NR	Case series	Germany	1	NR	Other (Catheterization lab)	Prospective data collection	43	NR/Unable to determine	NR/Unable to determine	Mean 10.4 (5.5) yr
Berger (2017)	Govt.	Prospective cohort, Retrospective cohort	United States	4	2006-2011	PICU (non-cardiac only)	Chart review Prospective data collection	99	Convenience	Neonates Infants	Mean 4.7 (3.0) vs. 4.7 (3.1) mo
Berner (1998)	Govt. NGO	Retrospective cohort	Germany	1	1993-1994	Other (Children's Hospital Neonatal ICU admission)	Chart review	136	NR/Unable to determine	Neonates	NR
Conroy (2016)	Govt. NGO	Secondary analysis of RCTs, including subgroup analysis	Uganda	1	NR	Hospital floor outside the ICU	Prospective data collection	180	NR/Unable to determine	Children	Median 2.0 [IQR 1.0-3.0] yr
Conroy (2012)	Govt.	Case/control study (case matched)	Malawi	1	1997-2009	Hospital floor outside the ICU	Chart review Prospective data collection	155	NR/Unable to determine	Infants Children Adolescents	Median 34 [IQR 27-51] mo
DeMeloBezerra Cavalcante (2016)	Govt.	Prospective cohort	Brazil	1	2013-2014	PCICU (cardiac only)	Prospective data collection	289	Consecutive	Neonates Infants Children Adolescents	Mean 3.0 (4.4) yr
Eaton (2014)	NR	Retrospective cohort	England	1	2002-2008	Operating room (OR)	Registry	123	NR/Unable to determine	Neonates	Mean 39.3 weeks gestational age (0.6)
Egerer (2000)	Govt.	Case series	Germany	1	NR	NR/Unable to determine	Chart review Prospective data collection	119	NR/Unable to determine	Children	Median 42.5 mo [range 18-78]

Emani (2013)	NR	Retrospective cohort	United States	1	2010-2012	PCICU (cardiac only)	Chart review Prospective data collection	512	Consecutive	Neonates	Thrombosis group Mean 8 (1) days, No thrombosis group Mean 7 (1) days
Emani (2013)	NR	Prospective cohort	United States	1	NR	PCICU (cardiac only)	Prospective data collection	28	NR/Unable to determine	Neonates	Mean 3 (1) day
Erdman (2011)	Govt. NGO Other (Charitable donation)	Retrospective cohort	Uganda	1	2007-2009	NR/Unable to determine	Chart review	156	Convenience	Infants Children	Overall NR
Fattah (2017)	Other (self)	Prospective cohort, Cross-sectional study	Saudi Arabia	1	2013-2015	Other (NICU)	Chart review, Prospective data collection	320	NR/Unable to determine	Neonates	NR
Fijnvandraat (1995	NR	Prospective cohort	The Netherlands	1	1990-1992	PICU of unknown composition	Prospective data collection	35	Consecutive	Infants Children Adolescents	Median 4.3 y [range 0.13-15]
Flori (2007)	Govt. NGO	Prospective cohort, Observation/ descriptive study	USA	2	1996-2000	PICU of unknown composition	Prospective data collection	320	NR/Unable to determine	Neonates Infants Children Adolescents	Mean 5.9 yr (6)
Flori (2003)	Govt.	Prospective cohort	United States	2	1996-1998	PICU of unknown composition	Prospective data collection	83	Consecutive	Neonates Infants Children Adolescents	Mean 5.2 (5.5) yr
Ganda (2018)	NR	Prospective cohort	Indonesia	1	2017-2017	Mixed PICU (cardiac and non-cardiac)	Prospective data collection	70	NR/Unable to determine	Infants Children Adolescents	The mean age in improved group was 6.38 yr and median was 4.6 yr, while in dying group mean was 4.87 and median 2.30 yr
Giuliano (2013)	Govt.	Prospective cohort, Observational/ descriptive study	USA	1	2009-2011	PICU of unknown composition	Prospective data collection	45	Consecutive	NR/Unable to determine	Median non-SIRS 10.0y [IQR 2.8-15.0]; SIRS 9.5 y [IQR 5.5-14.0]; severe sepsis 13.0y [IQR 8.5-15.0]
Giuliano (2008)	Govt.	Prospective cohort	USA	1	NR	PICU (cardiac only)	Chart review, Prospective data collection	48	Consecutive	Infants	Median 5.1 [IQR 1.7-34.2] mo

Hamed (2019)	NR	Case/control study (case matched)	Egypt	1	2016-2017	Other (NICU)	Chart review	90	Convenience	Neonates	Neonatal
Hassinger (2012)	NR	Prospective cohort	United States	1	2009-2010	PCICU (cardiac only)	Prospective data collection	100	Consecutive	Neonates Infants Children Adolescents	Elevated group median 4 [IQR 4-6.5] mo Normal group 61 [21-144] mo
Iguchi (2010)	NR	Case/control study (case matched), Prospective cohort	Japan	1	1996-2007	NR/Unable to determine	Chart review, Prospective data collection	151 (12 with VOD)	Consecutive	Neonates Infants Children Adolescents	Mean 7.8 yr [range 0-21] (SD not reported)
Jain (2011)	Govt. NGO	Case series	India	1	2004-2007	Hospital floor outside ICU	Chart review, Prospective data collection	183	NR/Unable to determine	Children	Healthy control median 25 [14-32], mild malaria 19 [12-36], cerebral malaria survivor 25 [12-40], cerebral malaria non-survivor 25 [13.5-37.5]
Kimura (2016)	Govt.	Randomized control trial (RCT), cross-over RTC, pragmatic RCT	USA	1	NR	PICU of unknown composition	Prospective data collection	35	Random	Neonates Infants Children Adolescents	
Levy (2003)	Govt. NGO	Prospective cohort	France	2	1993-1999	Other (Cardiac operating room)	Prospective data collection	17 Fontan patients, Good clinical outcome 8, Poor clinical outcome group 9 patients	Consecutive	Children Adolescents	Good outcome group median 10 [6-16] yr, poor outcome group median 3.5 [2-23] yr
Lin (2017)	NGO	Case/control study (case matched)	Taiwan	1	2012-2015	PICU of unknown composition	Prospective data collection	42 children with sepsis; 15 controls	NR/Unable to determine	Children	Median 4.1 yr [IQR 1.7-8.7]
Lo (2010)	NR	Prospective cohort, Observational/ descriptive study	United Kingdom	1	NR	PICU of unknown composition	Chart review, Prospective data collection	28	Consecutive	Infants Children Adolescents	8.59 yr [range 0.33-14.17]
Lo (2009)	NR	Prospective cohort, Observational/ descriptive study	United Kingdom	1	NR	PICU of unknown composition	Prospective data collection	28	Consecutive	NR/Unable to determine	median favorable outcomes (n=24) 7.92 [range 0.33-14.17]; unfavorable outcomes (n=4)

											10.50 [range, 2.33-13.42]
Lopes (1998)	NGO	Prospective cohort	Brasil	1	1993-1996	Other (Heart Institute)	Prospective data collection	30	Consecutive	Children Adolescents Adults	Median 25 yr [range 1.2-45]
Lovegrove (2009)	Govt. NGO	Case/control study (case matched)	Thailand and Uganda	2	NR	NR/Unable to determine	Registry	28 control, 67 uncomplicated malaria, 69 cerebral malaria	NR/Unable to determine	Children Adolescents	Median controls 7 yr [3.2-12]; malaria 7 [3-12]; cerebral malaria 5.4 [3.2-12]
Mankhambo (2010)	NGO	Prospective cohort, Observational/ descriptive study	Malawi	1	2004-2006	PICU of unknown composition	Chart review, Prospective data collection	293	NR/Unable to determine	Infants Children Adolescents	Median 2.4 yr [IQR 0.7-6.0]
Manyelo (2019)	Govt.	Case series	South Africa	1	2016-2017	Hospital floor outside the ICU	Prospective data collection	47	Consecutive	Infants Children Adolescents	Median 22 [IQR 10.5-57.0] mo
Mariko (2019)	Other (No funding)	Case series	Indonesia	1	NR	Hospital floor outside the ICU	Prospective data collection	110	Consecutive	Children Adolescents	
Meki (2003)	NR	Prospective cohort, Observational/ descriptive study	Egypt	1	2002-2002	PICU of unknown composition	Prospective data collection	46	NR/Unable to determine	Children Adolescents	2-13 yr
Melendez (2019)	NR	Retrospective cohort	USA	1	2012-2014	Emergency room (ER)	Chart review	94	NR/Unable to determine	Neonates Infants Children Adolescents	Sepsis 4.0 yr [IQR 1.8-11], septic shock 12.2 yr [IQR 8.1-16.3]
Moxon (2015)	NOG	Prospective cohort	Malawi	1	2008-2011	Other (Hospital)	Prospective data collection	140 cerebral malaria with retinopathy, 36 cerebral malaria without retinopathy, 14 non-malaria comatose children, 91 mild malaria, 85 non-malaria febrile illness and 36 healthy controls	Consecutive	Children	In mo: healthy controls 57 [39-94], Mild febrile illness 39 [24-62], uncomplicated malaria 65 [40-84], non-malaria coma 56 [31-64], retinopathy positive cerebral malaria 45 [28-52], retinopathy negative cerebral malaria 45 [33-62]
Murshid (2002)	NR	Case series	Saudi Arabia	1	NR	Other (ICU that treats children and adults)	Prospective data collection	Exclude study: only 5 children and unable to extract pediatric data	NR/Unable to determine	Children Adolescents	Unable to determine

Osmancik (2001)	Govt.	Case/control study (case matched)	Germany	1	1995-1999	PICU of unknown composition	Prospective data collection	50	NR/Unable to determine	Children	With bypass 7.7 (2.8) yr, without bypass 7.9 (3.2) yr
Padungmaneesub (2019)	NR	Case series	Thailand	1	2016-2016	PICU (non-cardiac only)	Prospective data collection	103	Consecutive	Infants Children Adolescents	3.8 yr (4.6)
Peker (2011)	Other (self)	Prospective cohort, Observational/ descriptive study	Turkey	1	NR	Other (NICU)	Prospective data collection	61	NR/Unable to determine	Neonates	Newborns
Phiri (2011)	NGO	Prospective cohort	Makawi	1	NR	NR/Unable to determine	Prospective data collection	100 children with cerebral malaria, 59 with mild malaria, 32 with fever bu no malaria, 20 health control children	Consecutive	Infants Children	Cerebral malaria: 34.5 [8.0-86.0], mild malaria 24.0 [3.0-60.0], non-malaria febrile controls 23.5 [6.0-60.0], non-febrile controls 23.0 [6.0-48.0]
Qiu (2017)	NR	Case/control study (case matched)	China	1	2012-2015	NR/Unable to determine	Prospective data collection	32 controls, 31 hand foot mouth no encephalitis, 41 HFM encephalitis, 21 HFM severe encephalitis	NR/Unable to determine	Infants Children	Mean 2.15 yr (0.61)
Samransamruajkit (2005)	Govt.	Case series, Observational/ descriptive study	Thailand	1	2000-2002	PICU of unknown composition	Chart review, Prospective data collection	16	NR/Unable to determine	Infants Children Adolescents	Conventional vent. Mean 8.4 (SE 1.6) yr HFO Mean 2.48 (SE 0.7) yr
Sanli (2012)	Industry	Prospective cohort	Turkey	1	2009-2009	Other (Catherization lab)	Prospective data collection	70	NR/Unable to determine	Infants Children Adolescents	Mo [range] 128.3 (87) [12 mo-26 yr] 104.2 (58) [2 mo-16 yr] 114.1 (53) [9 mo-16 yr]
Shaikh (2015)	Govt. NGO	Prospective cohort	Canada	1	NR	Other (Neonatal ICU)	Prospective data collection	12 asphyxiated and 4 healthy control newborns	Consecutive	Neonates	Mean 39.4 (0.85) weeks GA for controls, 39.1 (1.9) weeks GA for cases
Shi (1993)	NR	Case/control study (case matched)	China	1	1990-1993	PICU of unknown composition	Prospective data collection	30 healthy controls, 14 sepsis, 6 septic shock	NR/Unable to determine	Neonates	Median control 2.5 days [1-14], sepsis 3.5 days [1-27], shock 3 [1-7]
Shiraishi (2008)	NR	Case series, Observational/	Japan	6	1998-2007	NR/Unable to determine	Prospective data collection	132 (6 HUS without encephalopathy, 10 HUS with, 10 acute	NR/Unable to determine	Infants	Median [range] HUS with 5.2y [17m-13y], HUS

		descriptive study						colitis without HUS, 106 controls))			without 6.1y [18m-14y], acute colitis 6.3y [13m-12y], controls 6.4y [3m-15y]
Sosa-Bust (2011)	Govt.	Prospective cohort	Mexico	1	NR	PICU of unknown composition	Prospective data collection	118	Consecutive	Infants Children Adolescents	Sepsis (n=88) 3.5 mo [2.8-4.2]; controls (n=30) 2.9 mo [1.5-4.2]
Thampatty (2013)	Govt.	Prospective cohort	USA	1	NR	PICU (non-cardiac only)	Prospective data collection	19	Consecutive	Infants	Mean 6.1 (3.7) mo and 6.5 (4.7) mo
Tzanetos (2012)	Govt.	Case series	USA	1	NR	PCICU (cardiac only)	Prospective data collection	16	Consecutive	Neonates Infants Children Adolescents	Norwood mean 4.6 days (1.7), Glenn 154.3 days (26.5), Fontan 864.3 days (213.4)
Veleminsky (2008)	NR	Case series	Czech Republic	1	2005-2006	Other (delivery room)	Prospective data collection	152	NR/Unable to determine	Neonates NR/Unable to determine	Newborn
Vieira (2010)	Govt.	Prospective cohort	Brazil	1	2004-2005	PICU (non-cardiac only)	Prospective data collection	30	Consecutive	Neonates	27.7 days [IQR 12-50]
Vitkova (2018)	Govt.	Prospective cohort	Czech Republic	1	2017-2017	Other (ECMO Center)	Prospective data collection	26	NR/Unable to determine	Neonates	Newborns GA 38.9 (ECMO) to 39.4 (Control)
Wang (2014)	Govt.	Prospective cohort, Observational/ descriptive study	USA	1	2009-2011	PICU of unknown composition	Prospective data collection	45	Consecutive	Infants Children Adolescents	Median [IQR] non-SIRS10.0y [2.8-15.0]; SIRS 9.5y [5.5-14.0]; severe sepsis 13.0y [8.5-15.0]
Whalen (2000)	Govt.	Case/control study (case matched)	USA	1	NR	PICU (non-cardiac only)	Prospective data collection	77 sepsis/shock, 14 critically ill without sepsis	Consecutive	Neonates Infants Children Adolescents	Median 27 mo [1 day - 206 mo]
Wright (2018)	Govt.	Case/control study (case matched)	Bangladesh	1	2013-2014	Mixed PICU (cardiac and non-cardiac)	Prospective data collection	420	NR/Unable to determine	Neonates Infants	
Yıldırım (2014)	NR	Prospective cohort, Observational/ descriptive study	Turkey	1	2008-2009	PICU of unknown composition	Prospective data collection	42	NR/Unable to determine	Infants Children	L to R shunt no PAH 10.1 (1.1) [range 4-21] mo, L to R shunt with PAH 10.8 (5.4) [range 5-14] mo, L-R shunt with PAH and LCOS 6.8 (1.9) [range 4-11] mo

Zaki (2009)	NR	Prospective cohort, Observational/ descriptive study	Egypt	1	2007-2007	Other (NICU)	Prospective data collection	120	Consecutive	Neonates	Newborns
Zinter (2017)	Govt.	Prospective cohort	United States	5	2008-2015	PICU (non-cardiac only)	Prospective data collection	194 total, 38 non-survivors, 156 survivors	Consecutive	Infants Children Adolescents	4.9 [0.9-11.5] yr
Zinter (2016)	NR	Case series	USA	5	2008-2014	PICU of unknown composition	Prospective data collection	259	NR/Unable to determine	Infants Children Adolescents	Median 5.2 yr [1.1-13.2]

Abbreviations: Govt., government; NGO, nongovernmental organization; NR, not reported; PICU, pediatric intensive care unit; PCICU, pediatric cardiac intensive care unit; ; IQR, interquartile range; SD, standard deviation; mo, months; yr, years

[a]Neonates (0 to 30 days), Infants (31 days to < 1 year), Children (1 year to < 12 years), Adolescents (12 years to < 18 years)

[b]Data presented as mean (SD) or median [interquartile range, range]

Supplemental Table 2. Performance Characteristics for Assessment Tools and Scores for Endothelial Dysfunction in Critically Ill Children (n=62 studies)

Author (yr)	Score/Assessment Tool	Is this a study of score/tool derivation or validation?	Inclusion criteria	Timing of score/tool assessment	Outcomes	Performance Characteristics
Abo-Hagar (2017)	Serum/plasma biomarkers, Other (CRP, SAA)	Derivation	General PICU population (mixed cardiac and non-cardiac)	1st and 3rd day	Mortality, Other (Predicting VAP)	Se: CRP 83.33 (35.9-99.6) mg/ml, SAA 100 (54.1-100)ug/ml, sICAM1 100 (54.1-100)ng/mL Sp: CRP 72.41 (52.8-87.3) mg/ml, SAA 93.1 (77.2-99.2) ug/ml, sICAM1 179.31 (60.3-92) ng/mL PPV: CRP 38.4 (13.0-69.6) mg/ml, SAA 74.9 (32.0-97.5) ug/ml, sICAM1 49.9 (19.9-80.0) ng/mL NPV: CRP 95.5 (77.2-99.9) mg/ml, SAA 100 (87.2-100) ug/ml, sICAM1 100 (85.2-100) ng/mL AUROC: CRP 0.83 (0.66-0.93) mg/ml, SAA 0.97 (0.86-1.00) ug/ml, sICAM1 0.95 (0.82-0.99) ng/mL
Al Yaman (1996)	Other (Reactive Nitrogen Intermediates)	NR	Other (cerebral malaria)	Serum at admission	Mortality, Other (Coma severity and duration)	Other: Kruskall-Wallis nonparametric test: Coma score (2-4/0-1) vs RNI levels, p=0.008; duration >48h, p=0.046; death, p=0.014
Al-Bitalgi (2017)	Serum/plasma biomarkers	Validation	General PICU population (mixed cardiac and non-cardiac)	Day 1 and day 3	Organ-specific outcomes/residual morbidity	Se: Best cutoff value of plasma sICAM-1 level for prediction of death from ALI with the highest sensitivity (100%) specificity (83%) was 1000 ng/mL for sICAM-1 at day 3 with positive predictive value of 88%. AUROC: Area under the curve (AUC) was larger for the sICAM-1 level at day 3 than at day 1.
Apltz (2012)	Other (pulmonary endothelial function by vasodilator response to acetylcholine)	Validation	Other (idiopathic pulmonary arterial hypertension)	Day of procedure	Functional outcomes/residual morbidity	AUROC: The ROC curve analysis also was performed for reduction of mPAP-to-mSAP ratio and revealed a reduction of mPAP-to-mSAP ratio of 30% as the best cutoff value (area under the ROC curve: 0.753, 95% confidence interval: 0.603 to 0.904, sensitivity: 0.63, specificity: 0.81, p = 0.006)
Berger (2017)	Serum/plasma biomarkers	Other (Retrospective derivation, prospective validation)	General PICU population (only non-cardiac)	Not defined	Other (Set of biomarkers that predict presence of intracranial hemorrhage)	Se/Sp: Sensitivity and specificity for prediction of AHT was 95.8% (95% CI, 94.4-97.0) and 54.9% (95%CI, 50.9-58.9) at a cutoff of 0.182 AUROC: AUC s 0.906 (95% CI, 0.893-0.919).
Berner (1998)	Serum/plasma biomarkers	NR	Sepsis	Cord blood at birth	Other (Unable to determine since the Tables and Figures did not copy well)	Se/Sp: Unable to read Table 3
Conroy (2016)	Serum/plasma biomarkers	Validation	Other (Severe malaria)	Day 1, 2, 3, 4, 14	Mortality, Functional outcomes/residual morbidity	AUROC: Models including Ang-2 or sFlt-1 were significantly better than LODS alone at predicting in-hospital mortality with AUCs of 0.85 (95% CI, .79-.90; P = .03) and 0.83 (95% CI, .77-.88, P = .03)
Conroy (2012)	Serum/plasma biomarkers	Validation	Other (Cerebral malaria)	Day 1 of hospital admission	Mortality	Se: 93.2% sensitivity to predict death and a misclassification rate of 23.1% AUROC: 0.73 (95% CI: 0.65-0.79). aOR: 3.9 (1.2-12.7), p=0.024

DeMeloBezerraCavalcante (2016)	Serum/plasma biomarkers	Other (Investigational)	PCICU population (only cardiac)	NR	Organ-specific outcomes/residual morbidity	AUROC: post-op syndecan-1 predicts AKI (AUC 0.77, 0.05); post-op e-selectin predicts AKI (AUC 0.51, 0.05) post-op icam-1 predicts AKI (AUC0.57, 0.05)
Eaton (2014)	Serum/plasma biomarkers	NR	Other (Patients with surgical bowel sections with confirmed NEC)	Unable to determine	Mortality	NR
Egerer (2000)	Serum/plasma biomarkers	Derivation	General PICU population (mixed cardiac and non-cardiac), Sepsis, Other (SLE and pSS, patients with sepsis, different infectious diseases and healthy controls)	Day 1 or 2	Other patient-centered outcomes	Other: nonparametric Kruskal (Wallis test to compare the levels of sCD14, sE-selectin and sICAM-1 between the patient groups investigated. P-values of <0.05 were considered to be statistically significant.
Emani (2013)	NR	Other (Investigational)	PCICU population (only cardiac)	NR	Other (Presence of absence of thrombosis)	Other: Correlation. Significantly elevated plasminogen activator inhibitor 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) in SVP neonates with thrombosis compared with without thrombosis (p ¼ 0.04 and p ¼ 0.03, respectively
Emani (2013)	Serum/plasma biomarkers	Validation	PCICU population (only cardiac)	Preop	Other (Thrombosis)	AUROC: Area under the curve for PAI-1 = 0.762 (95% CI: 0.525 to 0.989; p = 0.04), TAFI = 0.786 (95% CI: 0.570 to 0.990; p = 0.03), TGA = 0.786 (95% CI: 0.592 to 0.980; p = 0.02) and for all 3 biomarkers combined, area under the curve = 0.908 (95% CI: 0.789 to 0.999; p = 0.001).
Erdman (2011)	Serum/plasma biomarkers	Derivation	Sepsis	Admission	Mortality, Other (Biomarker levels in uncomplicated vs severe malaria)	Se: Predicting mortality with severe malaria: Ang-2 >5.6 ng/mL 78.3% (56.3-87.1); sICAM-1 >645.3 ng/mL 87% (66.4-97.2); sFlt-1 >1066.3 pg/mL 82.6% (61.2-95); PCT >43.1 56.5% (34.5-76.8); IP-10 >831.2 pg/mL 82.6% (61.2-95); sTREM-1 >289.9pg/mL 95.7% (78.1-99.9) Sp: Same cutoffs: Ang-2 78.8% (68.2-87.1); sICAM-1 75% (64.1-84); sFlt-1 57.5% (45.9-68.5); PCT 82.5% (72.4-90.1); IP-10 85% (75.3-92); sTREM-1 43.8% (32.7-55.3) PPV: Ang-2 18.2% (5.8-38.7); sICAM-1 17.4% (5.9-35.9); sFlt-1 10.5% (3.4-23.1); PCT 16.3% (3.8-39.5); IP-10 25% (8.3-49.8); sTREM-1 9.3% (3.3-19.6) NPV: Ang-2 98.4% (92.4-99.9); sICAM-1 99% (932.-100); sFlt-1 98.2% (90.4-100); PCT 96.9% (90.5-99.5); IP-10 98.8% (93.4-100); sTREM-1 99.4% (90.5-100) LR: Ang-2 3.7 (2.9-4.7); sICAM-1 3.5 (2.8-4.3); sFlt-1 1.9 (1.5-2.5); PCT 3.2 (2.2-4.7); IP-10 5.5 (4.5-6.8); sTREM-1 1.7 (1.3-

						2.2)//Negative likelihood ratio: Ang-2 0.3 (0.1-0.7); sICAM-1 0.2 (0.06-0.5); sFlt-1 0.3 (0.1-0.8); PCT 0.5 (0.3-1); IP-10 0.2 (0.07-0.6); sTREM-1 0.1 (0.01-0.7) AUROC: Ang-2 0.83 (0.75-0.9); sICAM-1 0.84 (0.75-0.9); sFlt-1 0.75 (0.65-0.83); PCT 0.72 (0.62-0.8); IP-10 0.8 (0.71-0.87); sTREM-1 0.76 (0.66-0.84); Parasitemia 0.66 (0.56-0.75)
Fattah (2017)	Serum/plasma biomarkers	NR	Sepsis, Other (NICU admission)	Day 1 of symptoms	Other (not reported, results reported according to early or late sepsis vs. healthy)	Se: CRP 78%, IL6 83%, TNF 69%,E-selectin 73%, Procalcitonin 72% Sp: CRP 70%, IL6 68%, TNF 70%,E-selectin 60%, Procalcitonin 70% AUROC: CRP 0.85 (0.81-0.89), IL6 0.82 (0.76-0.87), TNF 0.82 (0.75-0.87),E-selectin 0.74 (0.68-0.79), Procalcitonin 0.81 (0.75-0.86)
Fijnvandraat (1995	Serum/plasma biomarkers	NR	General PICU population (mixed cardiac and non-cardiac)	Day 1	Mortality	Se: Protein C activity <10 100%; GMPS >12 78% Sp: Protein C activity <10 84%; GMPS >12 88% PPV: Protein C activity <10 60%; GMPS >12 70% NPV: Protein C activity <10 100%; GMPS >12 92% Other: Protein C activity <10 12.6 (1.9-181); GMPS >12 8.8 (2.2-117)
Flori (2007)	Serum/plasma biomarkers	NR	General PICU population (only non-cardiac)	vWF-Ag levels on day 1 and 2 of acute lung injury	Mortality, Other (Ventilator-free days)	aOR: vWF-Ag >450 day 1 of ALI and mortality 7.0 (0.99-49.3); >=2 organ dysfunction and mortality 14.2 (1.5-138.5)// vWF-Ag >450 11.2 (1.1-115); PRISM III 1.5 (1.1-1.9)
Flori (2003)	Serum/plasma biomarkers	Other (Investigational)	Other (PICU of unknown composition)	Day 1 and 2	Mortality, Organ-specific outcomes/residual morbidity	Other: Increased odds of dying:day 1: odds ratio [OR] 1.10, range 1.02-1.18, p .012; day 2: OR 1.18, range 1.05-1.32, p .004, for each 100-point increase in sICAM-1);
Ganda (2018)	Serum/plasma biomarkers	Derivation	General PICU population (mixed cardiac and non-cardiac), Sepsis	Serum sVCAM-1 on admission	Other (Development of sepsis)	Se: 100% for sVACM1 > 313 ng/mL Sp: 100% for sVACM1 >318 to >311 ng/mL PPV: 100% for sVACM1 >318 to >311 ng/mL NPV: 100% for sVACM1 > 313 ng/mL AUROC: 1.00 for sVACM1 >318 to >313 ng/mL
Giuliano (2013)	Serum/plasma biomarkers	Validation	General PICU population (only non-cardiac), Sepsis	Days 1-7	Outcomes related to MODS	Se: At the optimal cutoff for angpt-2 (3,955 pg/mL), there was a sensitivity of 76% for predicting more severe illness. Sp: At the optimal cutoff for angpt-2 (3,955 pg/mL), there was a specificity of 74% for predicting more severe illness. PPV: At the optimal cutoff for angpt-2 (3,955 pg/mL), there was a positive predictive value of 68% for predicting more severe illness. NPV: At the optimal cutoff for angpt-2 (3,955 pg/mL), there was a negative predictive value of 81% for predicting more severe illness. AUROC: The angpt-2 level alone on day 2 showed a significant AUC to distinguish between patients with severe sepsis/septic shock versus all others (AUC = 0.77 [95% CI, 0.61-0.93])

Giuliano (2008)	Serum/plasma biomarkers	Validation	PCICU population (only cardiac)	Hour 0 (after the termination of CPB), and at hours 6 and 24 following cessation of CPB	Other (Length of stay, outcome following CPB)	Other: Angpt-2 levels correlated significantly with cardiac intensive care unit (CICU) length of stay (LOS) and were an independent predictor for CICU LOS on subsequent multivariate analysis. Baseline angpt-2/-1 ratio (P = 0.004), 24 h post-CPB angpt-2/-1 ratio (P = 0.05), 24 h post-CPB angpt-2 (P = 0.006), and positive postoperative fluid balance (P\0.001) remained significant independent predictors of prolonged CICU LOS.
Hamed (2019)	Serum/plasma biomarkers	Derivation	Sepsis	1	Organ-specific outcomes/residual morbidity	Se: NO, MDA and TAO levels sensitivity (96.4%, 95%, and 98.8% respectively) Sp: NO, MDA and TAO levels specificity (93%, 92% and 94% respectively)
Hassinger (2012)	Serum/plasma biomarkers	Other (Investigational)	PCICU population (only cardiac)	Preoperative and post-operative assessment of ADMA	Organ-specific outcomes/residual morbidity	Other: Correlation
Iguchi (2010)	Serum/plasma biomarkers	NR	Other (Unable to determine)	Protein C level drawn day 0, 7, 14, 21, 28 post stem cell transplant	Other (Development of VOD)	Se: Protein C activity 34.5% was 100% sensitive Sp: Protein C activity 34.5% was 83.3% specific AUROC: Protein C activity 34.5% 0.939 (0.897-0.981)
Jain (2011)	Serum/plasma biomarkers	Validation	Other (Cerebral malaria)	Day 1	Mortality	AUROC: ANG-1 (AUC = 0.35), ANG-2 (AUC = 0.95) and ratio of ANG-2/ANG-1 (AUC = 0.90) were better markers to discriminate CMNS from MM cases.
Kimura (2016)	Serum/plasma biomarkers	Validation	General PICU population (only non-cardiac), Other (ARDS)	Day 0, 7	Other (Clinical outcome)	NR
Levy (2003)	Other (Histochemical analysis of eNOS protein in lung biopsy samples)	Other (Investigational)	Other (Fontan Patients undergoing takedown)	On takedown procedure	Other patient-centered outcomes	Other: Correlation to histochemical scores of eNOS protein level between groups
Lin (2017)	Serum/plasma biomarkers	NR	Sepsis	PICU Admission	Mortality, Outcomes related to MODS	AUROC: Serum thrombomodulin level and 1) septic shock AUC 0.867, cut off 4.71 mU/ml; 2) DIC 0.881, 5.71 mU/ml; 3) MODS 0.740, 4.71 mU/ml; 4) Mortality 0.863, 5.95 mU/ml
Lo (2010)	Serum/plasma biomarkers	Validation	General PICU population (only non-cardiac), Other (traumatic brain injury)	Day 1	Functional outcomes /residual morbidity	AUROC: L-selectin and IL-6 respectively having the highest and lowest AUC of 0.92 and 0.83

Lo (2009)	Serum/plasma biomarkers	Validation	General PICU population (only non-cardiac), Other (traumatic brain injury)	Day 1	Functional outcomes /residual morbidity	Se: L-selectin day 1 88%; IL-8 day 1 92%; NSE day 1 83%; S100B day 1 79%; IL-6 day 1 71%; Sp: L-selectin day 1 75%; IL-8 day 1 75%; NSE day 1 75%; S100B day 1 75%; IL-6 day 1 75% AUROC: L-selectin day 1 0.92; IL-8 day 1 0.88; NSE day 1 0.83; S100B day 1 0.83; IL-6 day 1 0.83 Other: multiple paired analysis performed as well. Two combinations using S100b as the "screening marker" and either L-selectin or IL-6 as the "varying marker" achieved an AUC of 0.98, and their specificity and sensitivity for unfavorable outcome prediction were 96% and 100%, respectively.
Lopes (1998)	Serum/plasma biomarkers	Other (Investigational)	PCICU population (only cardiac)	NR	Mortality	Other: Correlation. Elevated levels of vWF:Ag activity in patient with pulmonary hypertension and short term survival in patients with pulmonary hypertension
Lovegrove (2009)	Serum/plasma biomarkers	NR	NR	Admission	Mortality, Other (Cerebral malaria prediction)	Se: Ang-1 cutoff 15.05 ng/ml: 0.7 (0.58-0.79); ang-2 cutoff 0.39 ng/ml: 0.83 (0.72-0.9); ratio cutoff 0.052: 0.73 (0.61-0.82); TNF cutoff 81.1 pg/ml: 0.48 (0.36-0.61) Sp: Same cutoffs: ang-1 0.75 (0.63-0.83); ang-2 0.6 (0.48-0.71); 0.7 (0.58-0.79); 0.62 (0.49-0.74) LR: Positive LR: ang-1 2.7 (1.8-4.3); ang-2 2.1 (1.5-2.8); ratio 2.4 (1.6-3.6); TNF 1.3 (0.84-2)//Neg LR ang-1 0.4 (0.28-0.6); ang-2 0.29 (0.17-0.51); ratio 0.39 (0.26-0.59); TNF 0.82 (0.6-1.1) AUROC: Malaria vs Cerebral malaria: ang-1 0.785 (0.709-0.861); ang-2 0.688 (0.595-0.780); ang-2/1 ratio 0.779 (0.702-0.856); TNF 0.557 (0.753-0.661) aOR: Ang-1 0.899 ng/ml (0.864-0.934)
Mankhambo (2010)	Serum/plasma biomarkers	Validation	Sepsis	Day 1	Mortality	aOR: Association with mortality
Manyelo (2019)	Serum/plasma biomarkers	Derivation	Other (TB meningitis)	NR	NR	Se: adult 7-marker biosignature in which transthyretin was replaced by NCAM1 73.9% Sp: adult 7-marker biosignature in which transthyretin was replaced by NCAM1 66.7% AUROC: adult 7-marker biosignature in which transthyretin was replaced by NCAM1 0.80
Mariko (2019)	Other (Angiopoietin-2)	Derivation	Other (Dengue fever)	NR	Organ-specific outcomes/residual morbidity	Se: 56.40% Sp: 58.30% AUROC: 63.40%
Meki (2003)	Serum/plasma biomarkers	Validation	General PICU population (only non-cardiac), Other (scorpion envenomed children)	Day 1	Other (Dysregulation of apoptosis)	NR
Melendez (2019)	Serum/plasma biomarkers	Derivation	Sepsis	1	Outcomes related to MODS	Other: P-value

Moxon (2015)	Serum/plasma biomarkers	Other (Investigational)	General PICU population (only non-cardiac)	Admission	Mortality, Other (Presence of retinopathy)	Other: Correlation, only soluble thrombomodulin was significantly increased in non-survivors
Murshid (2002)	NR	NR	NR	NR	NR	NR
Osmancik (2001)	Serum/plasma biomarkers	Other (descriptive)	Other (cardiac surgery	Pre-op, OR, Post-op	Other (No specific outcome. Descriptive study)	Other: Comparing levels between bypass vs. no bypass during cardiac surgery
Padungmaneesub (2019)	Serum/plasma biomarkers	Derivation	General PICU population (only non-cardiac)	1	Outcomes related to MODS	AUROC: Adding antithrombin to DIC score was better than the original score for predict mortality [area under curve (AUC) = 0.662 vs AUC = 0.65] and bleeding (AUC = 0.751 vs AUC = 0.732).
Peker (2011)	Serum/plasma biomarkers	Validation	Sepsis, Other (NICU)	Day 1	Functional outcomes/residual morbidity	Other: Comparing levels between patient populations
Phiri (2011)	Serum/plasma biomarkers	Other (Investigational)	General PICU population (only non-cardiac)	Admission, 2 and 30 days	Mortality, Other (presence of retinopathy)	Other: Correlation
Qiu (2017)	Serum/plasma biomarkers	NR	NR	Acute and recovery phase but this was not defined	Organ-specific outcomes, Other (predicting encephalitis)	Se: Predicting HFMD with encephalitis: serum/CSF neuron specific enolase cutoffs 16.3/20.1: 83.87/90.32%; serum/CSF VCAM-1 cutoffs 429.3/24.3: 75.81/80.65%; serum NSE+VCAM 12.3+498.4: 72.6%; CSF NSE+VCAM 25.2+27.5: 75.8% Sp: Serum/CSF NSE 82.8/81.72%; serum/CSF VCAM 87.1/83.87%; serum NSE+VCAM 76.34%; CSF NSE+VCAM 75.27% PPV: Serum/CSF NSW 79.03/85.5; serum/CSF VCAM 82.3/77.4; serum NSE+VCAM 71; CSF NSE+VCAM 74.2 NPV: Serum/CSF NSE 70.5/77.5; serum/CSF VCAM 75.6/68.9; serum NSE+VCAM 63.3; CSF NSE+VCAM 66 AUROC: Serum/CSF NSE 0.908(0.84-0.975)/0.958(0.92-0.997); serum/CSF VCAM 0.886(0.782-0.95)/0.897(0.829-0.965); serum NSE+VCAM 0.963(0.924-1); CSF NSE+VCAM 0.988(0.966-1) Youden's index: Serum NSE > 16.3 µg/L, CSF NSE > 20.1 µg/L, serum VCAM-1 > 429.3 µg/L, and CSF VCAM-1 > 24.3 µg/L
Samransamruajkit (2005)	Serum/plasma biomarkers	Validation	General PICU population (mixed cardiac and non-cardiac), Other (ARDS)	days 1, 3, 5 and 7 of ARDS	Mortality	LR: 11.9, $p < 0.001$

Sanli (2012)	Serum/plasma biomarkers	Validation	Other (Pulmonary hypertension associated with congenital heart disease)	Day 1	Functional outcomes/residual morbidity	Se: Pulmonary hypertension association homocysteine sensitivity of 83%; ADMA sensitivity of 70%; NO sensitivity of 50% Sp: Pulmonary hypertension association homocysteine specificity of 50%; ADMA specificity of 50%; NO specificity of 65% PPV: Pulmonary hypertension association homocysteine positive predictive value of 73%; ADMA positive predictive value of 72%; NO positive predictive value of 68% NPV: Pulmonary hypertension association homocysteine negative predictive value was 69%; ADMA negative predictive value of 57%; NO negative predictive value of 46%. AUROC: Pulmonary hypertension association homocysteine area under the ROC curve was 84.1 % (P = 0.001); ADMA area under the ROC curve was 63.4 % (P = 0.11); NO area under the ROC curve was 57 % (P = 0.406)
Shaikh (2015)	Serum/plasma biomarkers	Other (Investigational)	Other (Neonatal ICU)	Admission through 96 hours	Other (Correlation with brain injury assessed by MRI)	NR
Shi (1993)	Serum/plasma biomarkers	NR	Sepsis, Other (PICU)	Sepsis median 2 days (1-10), shock 1 day (1-2)	Organ-specific outcomes/residual morbidity	NR
Shiraishi (2008)	Serum/plasma biomarkers	Other (descriptive)	Other (HUS, colitis)	day 2.2 (1.0 (range: 1 to 4 days)	Other (predicting neurological complications)	Other: Comparing levels between patient populations
Sosa-Bust (2011)	Serum/plasma biomarkers	Validation	General PICU population (only non-cardiac), Sepsis	Day 1, 3, 7	Mortality	Other: Logistic regression analysis: ΔICAM-1 > 250 ng/mL from day 1 to 3: coefficient 0.22, p=0.01
Thampatty (2013)	Other (CSF sampling of non-specific endothelial biomarker byproduct)	Other (Investigational)	General PICU population (only non-cardiac)	Days 1, 2, and 3 of PICU admission	Other (Increased ADMA in CSF of TBI patients, hypothermia decreased CSF ADMA levels)	NR
Tzanetos (2012)	Serum/plasma biomarkers	NR	PCICU population (only cardiac)	POD 1, 3, 5, 10, 20, 30, 40	Other (Development of thrombus)	NR
Veleminsky (2008)	Serum/plasma biomarkers	Validation	Other (neonates preterm labor)	Day 1 (birth)	Other (Onset of neonatal sepsis)	Se: IL-6 0.800; TNF-alpha 0.364; IL-8 0.875 and sICAM-1 0.833 and 0.952 Sp: IL-6 0.972; TNF-alpha 0.943; IL-8 0.965; and sICAM-1 0.952
Vieira (2010)	Serum/plasma biomarkers	Other (Investigational)	Other (Infants with RSV bronchiolitis)	Admission	Other (Clinical score, duration of oxygen therapy, duration of	Other: Correlation

					mechanical ventilation)	
Vitkova (2018)	Serum/plasma biomarkers	Derivation	Other (Infants on ECMO compared to healthy controls)	First week of life	NR	Other: Increase in pro-inflammatory markers in ECMO group
Wang (2014)	Serum/plasma biomarkers	NR	General PICU population (only non-cardiac), Sepsis	NR	Functional outcomes/residual morbidity	PPV: Ang-1 0.384; Ang-2 0.625; Ang-2/Ang-1 0.760; VEGF 0.424 NPV: Ang-1 0.566; Ang-2 0.690; Ang-2/Ang-1 0.675; VEGF 0.764 Other: Canonical Correlation Analysis with the Forward Selection and Random Forests methods identified a particular set of biomarkers that included Angiopoietin-1 (Ang-1), Angiopoietin-2 (Ang-2), and Bicarbonate (HCO3) as having the strongest correlations with sepsis severity.
Whalen (2000)	Serum/plasma biomarkers	NR	General PICU population (only non-cardiac)	Admission and day 3	Mortality, Outcomes related to MODS	NR
Wright (2018)	Serum/plasma biomarkers	Derivation	General PICU population (mixed cardiac and non-cardiac)	NR	Mortality, Other (Development of sepsis)	aOR: Median Angpt-2:1 ratio was 0.48 [IQR: 0.25, 0.87] among infants who died compared to 0.21 [IQR: 0.10, 0.31] among survivors (aOR 2.29, p = 0.016
Yıldırım (2014)	Serum/plasma biomarkers	Validation	PCICU population (only cardiac)	Preop, postop day 1 and 5	Organ-specific outcomes/residual morbidity	Se: sICAM-0 concentration >359 ng/mL, there was a sensitivity of 90% and specificity of 95% for identification of LCOS in patients with L-R shunt and PAH AUROC: AUC: 0.98, 95% CI: 0.95-1.02, p<0.01
Zaki (2009)	Serum/plasma biomarkers	NR	NR	NR	Functional outcomes/residual morbidity	Se: Laboratory Markers in Early Diagnosis of Neonatal Sepsis C-reactive protein 86%; sE-selectin 59%; CRP+ sE-selectin 45%. Sp: Laboratory Markers in Early Diagnosis of Neonatal Sepsis C-reactive protein 97%; sE-selectin 87%; CRP+ sE-selectin 100% PPV: Laboratory Markers in Early Diagnosis of Neonatal Sepsis C-reactive protein 96%; sE-selectin 81%; CRP+ sE-selectin 100%. NPV: Laboratory Markers in Early Diagnosis of Neonatal Sepsis C-reactive protein 88%; sE-selectin 69%; CRP+ sE-selectin 65%.
Zinter (2017)	Serum/plasma biomarkers	Derivation	General PICU population (only non-cardiac)	Days 1, 2, 3, 4, 5	Mortality	AUROC: AUROC for the model including the OI, interleukin (IL)-8, and tumor necrosis factor (TNF)-R2 (gray line) was of 0.77 (95% CI, 0.70-0.83). The AUROC for the expanded model including the OI, IL-6, IL-8, IL-10, TNF-R2, and hematopoietic cellular transplantation (HCT) history (black line) was of 0.79 (95% CI, 0.72-0.86)

						Other: Correlation of elevated levels of cytokines with death: IL-6 p=0.013, IL-8 p=0.001, IL-18 p=0.037, IL-10 p=0.045 and TNF-R2 p=0.045
Zinter (2016)	Serum/plasma biomarkers	NR	General PICU population (only non-cardiac), Sepsis	Days 1 and 3	Mortality	aOR: Odds of Mortality day 1 ang-2: 3.7(1.2-11.5); day 3 ang-2: 10.2 (2.2-46.5); rising Ang-2: 3.3 (1.2-9.2)//All cause PICU mortality ang-2 day 1 4.0(1.3-11.6), day 3 ang-2 13(2.8-60.9)//all cause hospital mortality day 1 ang-2 3(1.1-8.1), day 3 ang-2 10.9(2.5-47.5)

Abbreviations: Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; AUROC, area under the receiver operating characteristics curve; aOR, adjusted odds ratio; PICU, pediatric intensive care unit; PCICU, pediatric cardiac intensive care unit

References

1. Abo-Hagar H, Abo-Elezz A, Mehrez M, Mabrouk MM, Elshora OA. Diagnostic Efficacy of Serum Amyloid A Protein and Soluble Intercellular Adhesion Molecule 1 in Pediatric Ventilator-Associated Pneumonia. J Intensive Care Med. 2017:885066617702598.
2. Al Yaman FM, Mokela D, Genton B, Rockett KA, Alpers MP, Clark IA. Association between serum levels of reactive nitrogen intermediates and coma in children with cerebral malaria in Papua New Guinea. Trans R Soc Trop Med Hyg. 1996;90(3):270-3.
3. Al-Biltagi M, Abo-Elezz A, Abu-Ela K, Suliman GA, Sultan TGH. The Prognostic Value of Soluble Intercellular Adhesion Molecule 1 Plasma Level in Children With Acute Lung Injury. J Intensive Care Med. 2017;32(5):320-5.
4. Apitz C, Zimmermann R, Kreuder J, Jux C, Latus H, Pons-Kuhnemann J, et al. Assessment of pulmonary endothelial function during invasive testing in children and adolescents with idiopathic pulmonary arterial hypertension. J Am Coll Cardiol. 2012;60(2):157-64.
5. Berger RP, Pak BJ, Kolesnikova MD, Fromkin J, Saladino R, Herman BE, et al. Derivation and Validation of a Serum Biomarker Panel to Identify Infants With Acute Intracranial Hemorrhage. JAMA pediatrics. 2017;171(6):e170429.
6. Berner R, Niemeyer CM, Leititis JU, Funke A, Schwab C, Rau U, et al. Plasma levels and gene expression of granulocyte colony-stimulating factor, tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, and soluble intercellular adhesion molecule-1 in neonatal early onset sepsis. Pediatr Res. 1998;44(4):469-77.
7. Conroy AL, Glover SJ, Hawkes M, Erdman LK, Seydel KB, Taylor TE, et al. Angiopoietin-2 levels are associated with retinopathy and predict mortality in Malawian children with cerebral malaria: a retrospective case-control study*. Crit Care Med. 2012;40(3):952-9.
8. Conroy AL, Hawkes M, McDonald CR, Kim H, Higgins SJ, Barker KR, et al. Host Biomarkers Are Associated With Response to Therapy and Long-Term Mortality in Pediatric Severe Malaria. Open forum infectious diseases. 2016;3(3):ofw134.
9. De Melo Bezerra Cavalcante, C. T., Castelo Branco KM, Pinto Júnior VC, Meneses GC, De Oliveira Neves, F. M., De Souza, N. M. G., et al. Syndecan-1 improves severe acute kidney injury prediction after pediatric cardiac surgery. J Thorac Cardiovasc Surg. 2016;152(1):178-86.
10. Eaton S, Sebire N, Thyoka M, Pierro A. Histologic and immunohistochemical features associated with outcome in neonatal necrotizing enterocolitis. European journal of pediatric surgery : official journal of Austrian Association of Pediatric Surgery et al] = Zeitschrift fur Kinderchirurgie. 2014;24(1):51-6.
11. Egerer K, Feist E, Rohr U, Pruss A, Burmester GR, Dorner T. Increased serum soluble CD14, ICAM-1 and E-selectin correlate with disease activity and prognosis in systemic lupus erythematosus. Lupus. 2000;9(8):614-21.
12. Emani S, Zurakowski D, Baird CW, Pigula FA, Trenor C, 3, Emani SM. Hypercoagulability markers predict thrombosis in single ventricle neonates undergoing cardiac surgery. Ann Thorac Surg. 2013;96(2):651-6.
13. Emani S, Zurakowski D, Baird CW, Pigula FA, Trenor C, 3, Emani SM. Hypercoagulability panel testing predicts thrombosis in neonates undergoing cardiac surgery. Am J Hematol. 2014;89(2):151-5.
14. Erdman LK, Dhabangi A, Musoke C, Conroy AL, Hawkes M, Higgins S, et al. Combinations of host biomarkers predict mortality among Ugandan children with severe malaria: a retrospective case-control study. PloS one. 2011;6(2):e17440.
15. Fattah MA, Omer AF, Asaif S, Manlulu R, Karar T, Ahmed A, et al. Utility of cytokine, adhesion molecule and acute phase proteins in early diagnosis of neonatal sepsis. Journal of natural science, biology, and medicine. 2017;8(1):32-9.
16. Fijnvandraat K, Derkx B, Peters M, Bijlmer R, Sturk A, Prins MH, et al. Coagulation activation and tissue necrosis in meningococcal septic shock: severely reduced protein C levels predict a high mortality. Thromb Haemost. 1995;73(1):15-20.

17. Flori HR, Ware LB, Glidden D, Matthay MA. Early elevation of plasma soluble intercellular adhesion molecule-1 in pediatric acute lung injury identifies patients at increased risk of death and prolonged mechanical ventilation. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2003;4(3):315-21.
18. Flori HR, Ware LB, Milet M, Matthay MA. Early elevation of plasma von Willebrand factor antigen in pediatric acute lung injury is associated with an increased risk of death and prolonged mechanical ventilation. Pediatric Critical Care Medicine. 2007;8(2):96-101.
19. Ganda IJ, Ali I, Lawang SA, Daud D. The prognostic value of soluble vascular cell adhesion molecules-1 (sVCAM-1) in children with septic shock. Current Pediatric Research. 2018;22(2):131-6.
20. Giuliano JS, J., Lahni PM, Bigham MT, Manning PB, Nelson DP, Wong HR, et al. Plasma angiopoietin-2 levels increase in children following cardiopulmonary bypass. Intensive Care Med. 2008;34(10):1851-7.
21. Giuliano JS, J., Tran K, Li FY, Shabanova V, Tala JA, Bhandari V. The temporal kinetics of circulating angiopoietin levels in children with sepsis. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2014;15(1):1.
22. Hamed AMM, Hassan AEA, Aladawy MAA, Hassan MH. Circulating nitric oxide, malondialdehyde and total antioxidant capacity levels among term septic neonates. Current Pediatric Research. 2019;23(2):106-11.
23. Hassinger AB, Wainwright MS, Lane JC, Haymond S, Backer CL, Wald E. Elevated preoperative serum asymmetrical dimethylarginine (ADMA) is associated with poor outcomes after pediatric cardiac surgery. Intensive Care Med. 2012;38(10):1697-704.
24. Iguchi A, Kobayashi R, Kaneda M, Kobayashi K. Plasma protein C is a useful clinical marker for hepatic veno-occlusive disease (VOD) in stem cell transplantation. Pediatric blood & cancer. 2010;54(3):437-43.
25. Jain V, Lucchi NW, Wilson NO, Blackstock AJ, Nagpal AC, Joel PK, et al. Plasma levels of angiopoietin-1 and -2 predict cerebral malaria outcome in Central India. Malaria journal. 2011;10:383.
26. Kimura D, Saravia J, Rovnaghi CR, Meduri GU, Schwingshackl A, Cormier SA, et al. Plasma Biomarker Analysis in Pediatric ARDS: Generating Future Framework from a Pilot Randomized Control Trial of Methylprednisolone: A Framework for Identifying Plasma Biomarkers Related to Clinical Outcomes in Pediatric ARDS. Frontiers in pediatrics. 2016;4:31.
27. Levy M, Danel C, Laval AM, Leca F, Vouhe PR, Israel-Biet D. Nitric oxide synthase expression by pulmonary arteries: a predictive marker of Fontan procedure outcome? J Thorac Cardiovasc Surg. 2003;125(5):1083-90.
28. Lin JJ, Hsiao HJ, Chan OW, Wang Y, Hsia SH, Chiu CH. Increased serum thrombomodulin level is associated with disease severity and mortality in pediatric sepsis. PloS one. 2017;12(8):e0182324.
29. Lo TYM, Jones PA, Minns RA. Pediatric brain trauma outcome prediction using paired serum levels of inflammatory mediators and brain-specific proteins. J Neurotrauma. 2009;26(9):1479-87.
30. Lo TYM, Jones PA, Minns RA. Combining coma score and serum biomarker levels to predict unfavorable outcome following childhood brain trauma. J Neurotrauma. 2010;27(12):2139-45.
31. Lopes AA, Maeda NY, Bydlowski SP. Abnormalities in circulating von Willebrand factor and survival in pulmonary hypertension. Am J Med. 1998;105(1):21-6.
32. Lovegrove FE, Tangpukdee N, Opoka RO, Lafferty EI, Rajwans N, Hawkes M, et al. Serum angiopoietin-1 and -2 levels discriminate cerebral malaria from uncomplicated malaria and predict clinical outcome in African children. PloS one. 2009;4(3):e4912.

33. Mankhambo LA, Banda DL, Jeffers G, White SA, Balmer P, Nkhoma S, et al. The role of angiogenic factors in predicting clinical outcome in severe bacterial infection in Malawian children. Crit Care. 2010;14(3):R91.
34. Manyelo CM, Solomons RS, Snyders CI, Mutavhatsindi H, Manngo PM, Stanley K, et al. Potential of host serum protein biomarkers in the diagnosis of tuberculous meningitis in children. Frontiers in Pediatrics. 2019;7.
35. Mariko R, Darwin E, Yanwirasti Y, Hadinegoro SR. The difference of angiopoietin-2 levels between dengue hemorrhagic fever patients with shock and without shock. Open Access Macedonian Journal of Medical Sciences. 2019;7(13):2119-22.
36. Meki AR, Hasan HA, El-Deen Z, Bakkar S. Dysregulation of apoptosis in scorpion envenomed children: its reflection on their outcome. Toxicon : official journal of the International Society on Toxinology. 2003;42(3):229-37.
37. Melendez E, Whitney JE, Norton JS, Silverman M, Harju-Baker S, Mikacenic C, et al. Systemic Angiopoietin-1/2 Dysregulation in Pediatric Sepsis and Septic Shock. Int J Med Sci. 2019;16(2):318-23.
38. Moxon CA, Chisala NV, Mzikamanda R, Maccormick I, Harding S, Downey C, et al. Laboratory evidence of disseminated intravascular coagulation is associated with a fatal outcome in children with cerebral malaria despite an absence of clinically evident thrombosis or bleeding. Journal of Thrombosis and Haemostasis. 2015;13(9):1653-64.
39. Murshid WR, Gader AG. The coagulopathy in acute head injury: comparison of cerebral versus peripheral measurements of haemostatic activation markers. Br J Neurosurg. 2002;16(4):362-9.
40. Osmancik P, Hambsch J, Schneider P, Bellinghausen W, Tarnok A. Soluble endothelial adhesion molecules during paediatric cardiovascular surgery with or without cardiopulmonary bypass. Cardiol Young. 2002;12(2):130-7.
41. Padungmaneesub W, Reungrongrat S, Manowong S, Fanhchaksai K, Panyasit N, Natesirinilkul R. Biomarkers of disseminated intravascular coagulation in pediatric intensive care unit in Thailand. Int J Lab Hematol. 2019;41(1):32-8.
42. Peker E, Akbayram S, Geylani H, Dogan M, Kirimi E. Global fibrinolytic capacity in neonatal sepsis. Clinical and Applied Thrombosis/Hemostasis. 2011;17(6):E64-9.
43. Phiri HT, Bridges DJ, Glover SJ, van Mourik JA, de Laat B, M'Baya B, et al. Elevated plasma von Willebrand factor and propeptide levels in Malawian children with malaria. PloS one. 2011;6(11):e25626.
44. Qiu S, Jiang L, Jiang W, Wang J. Significance of NSE and VCAM-1 in children with hand foot mouth disease combined with encephalitis. International Journal of Clinical and Experimental Medicine. 2017;10(1):1108-14.
45. Samransamruajkit R, Prapphal N, Deelodegenavong J, Poovorawan Y. Plasma soluble intercellular adhesion molecule-1 (sICAM-1) in pediatric ARDS during high frequency oscillatory ventilation: a predictor of mortality. Asian Pacific journal of allergy and immunology. 2005;23(4):181-8.
46. Sanli C, Oguz D, Olgunturk R, Tunaoglu FS, Kula S, Pasaoglu H, et al. Elevated homocysteine and asymmetric dimethyl arginine levels in pulmonary hypertension associated with congenital heart disease. Pediatr Cardiol. 2012;33(8):1323-31.
47. Shaikh H, Boudes E, Khoja Z, Shevell M, Wintermark P. Angiogenesis dysregulation in term asphyxiated newborns treated with hypothermia. PLoS ONE. 2015;10(5).
48. Shi Y, Li HQ, Shen CK, Wang JH, Qin SW, Liu R, et al. Plasma nitric oxide levels in newborn infants with sepsis. J Pediatr. 1993;123(3):435-8.
49. Shiraishi M, Ichiyama T, Matsushige T, Iwaki T, Iyoda K, Fukuda K, et al. Soluble tumor necrosis factor receptor 1 and tissue inhibitor of metalloproteinase-1 in hemolytic uremic syndrome with encephalopathy. J Neuroimmunol. 2008;196(1-2):147-52.

50. Sosa-Bustamante G, Amador-Licona N, Barbosa-Sabanero G, Guizar-Mendoza J, Lopez-Briones S, Mulgado-Aguas C, et al. Intercellular adhesion molecules and mortality for sepsis in infants younger than 1 year of life. Rev Invest Clin. 2011;63(6):601-6.
51. Thampatty BP, Klamerus MM, Oberly PJ, Feldman KL, Bell MJ, Tyler-Kabara E, et al. Hypothermia decreases cerebrospinal fluid asymmetric dimethylarginine levels in children with traumatic brain injury. Pediatric Critical Care Medicine. 2013;14(4):403-12.
52. Tzanetos DRT, Yu C, Hernanz-Schulman M, Barr FE, Brown NJ. Prospective study of the incidence and predictors of thrombus in children undergoing palliative surgery for single ventricle physiology. Intensive Care Med. 2012;38(1):105-12.
53. Veleminsky M, J., Stransky P, Veleminsky M, S., Tosner J. Relationship of IL-6, IL-8, TNF and sICAM-1 levels to PROM, pPROM, and the risk of early-onset neonatal sepsis. Neuro endocrinology letters. 2008;29(3):303-11.
54. Vieira RA, Diniz EM, Ceccon ME. Correlation between inflammatory mediators in the nasopharyngeal secretion and in the serum of children with lower respiratory tract infection caused by respiratory syncytial virus and disease severity. Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia. 2010;36(1):59-66.
55. Vitkova V, Panek M, Janec P, Sibikova M, Vobruba V, Haluzik M, et al. Endothelial Microvesicles and Soluble Markers of Endothelial Injury in Critically Ill Newborns. Mediators Inflamm. 2018;2018:1975056.
56. Wang K, Bhandari V, Giuliano JS, J., CS OH, Shattuck MD, Kirby M. Angiopoietin-1, angiopoietin-2 and bicarbonate as diagnostic biomarkers in children with severe sepsis. PloS one. 2014;9(9):e108461.
57. Whalen MJ, Doughty LA, Carlos TM, Wisniewski SR, Kochanek PM, Carcillo JA. Intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 are increased in the plasma of children with sepsis-induced multiple organ failure. Crit Care Med. 2000;28(7):2600-7.
58. Wright JK, Hayford K, Tran V, Al Kibria GM, Baqui A, Manajjir A, et al. Biomarkers of endothelial dysfunction predict sepsis mortality in young infants: a matched case-control study. BMC Pediatr. 2018;18(1):118.
59. Yildirim A, Guzelmeric F, Oner CN, Karaagac AT, Sasmazel A, Erdem H, et al. Prognostic significance of sICAM-1 and sVCAM-1 molecules for cardiac surgery in pediatric patients with pulmonary hypertension. Anadolu kardiyoloji dergisi : AKD = the Anatolian journal of cardiology. 2014;14(3):274-9.
60. Zaki Mel S, el-Sayed H. Evaluation of microbiologic and hematologic parameters and E-selectin as early predictors for outcome of neonatal sepsis. Arch Pathol Lab Med. 2009;133(8):1291-6.
61. Zinter MS, Spicer A, Orwoll BO, Alkhouli M, Dvorak CC, Calfee CS, et al. Plasma angiopoietin-2 outperforms other markers of endothelial injury in prognosticating pediatric ARDS mortality. American journal of physiology Lung cellular and molecular physiology. 2016;310(3):224.
62. Zinter MS, Orwoll BE, Spicer AC, Alkhouli MF, Calfee CS, Matthay MA, et al. Incorporating Inflammation into Mortality Risk in Pediatric Acute Respiratory Distress Syndrome. Crit Care Med. 2017;45(5):858-66.