Hematologic Dysfunction Criteria in Critically Ill Children:

The PODIUM Consensus Conference

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Data Supplement

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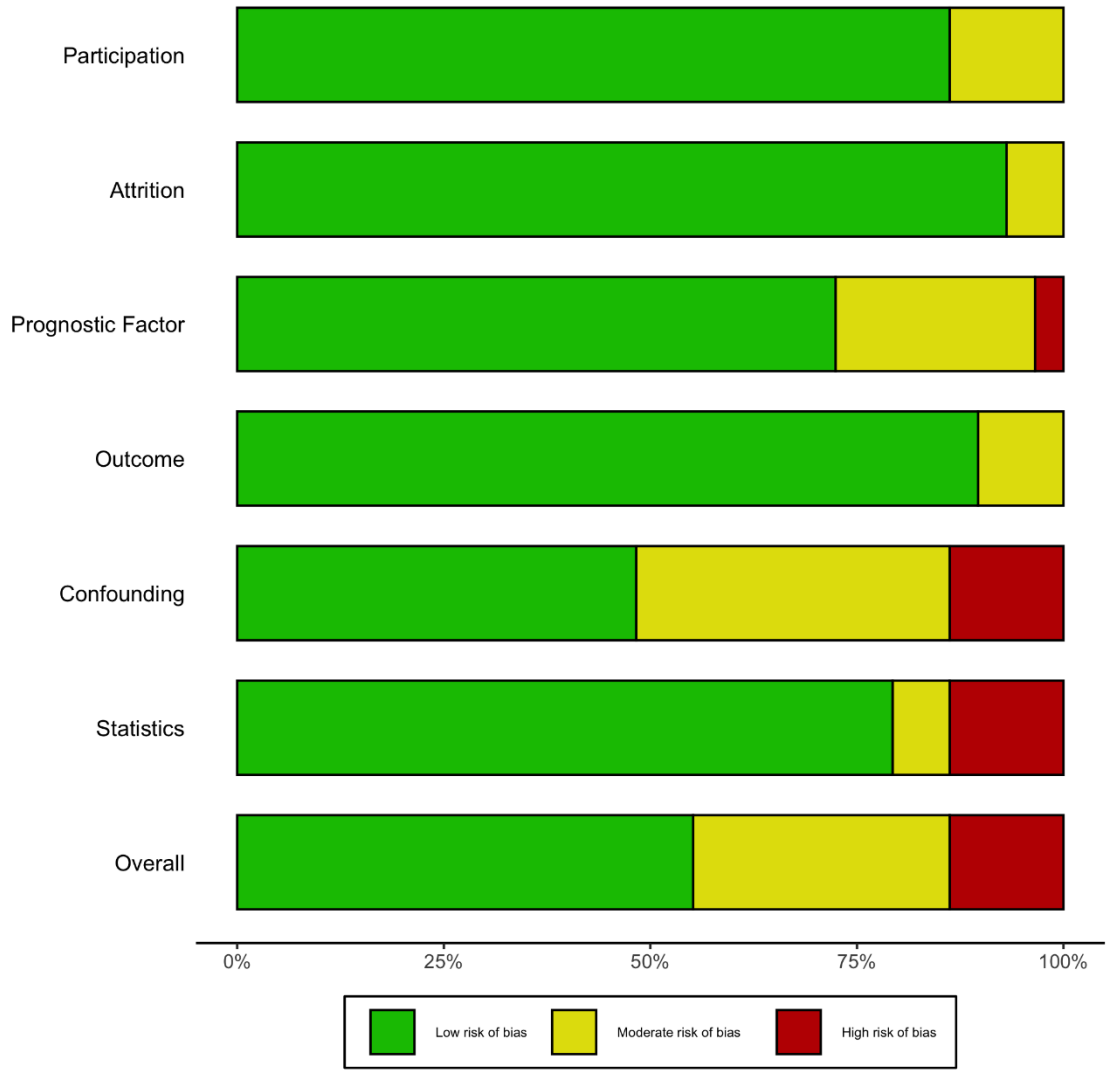

Supplemental Table 1. Studies Included in the PODIUM Hematologic Dysfunction Systematic Review (n=29 studies)

Author (yr)	Funding	Study design	Location	No. of sites	Study start year	Study end year	Setting	Data source(s)	Sample size	Recruitment	Age categories[a]	Age details[b]
An 2016	Govt.	Retrospective cohort	China	1	2000	2012	PICU of unknown composition	Chart review	29	Consecutive	Infants	Median 6 yr [range 0.5-16]
Bestati 2010	Govt.	Prospective cohort	France, Canada, Switzerland	7	1998	2000	PICU of unknown composition	Prospective data collection	1806	Consecutive	Children	525 infants aged 1 mo to < 1 yr; 853 children aged 1 yr to < 12 yr; 257 adolescents aged 12 yr to < 18 yr
Castellanos-Ortega 2002	NR	Retrospective cohort	Spain	14	1983	1995	PICU of unknown composition	Chart review	350	Consecutive	Adolescents	Mean 30.9 (2.27) (derivation cohort) 33.3 (3.04) (validation cohort)
Chhangani 2015	NR	Prospective cohort	India	1	2012	2013	PICU of unknown composition	Prospective data collection	100	Consecutive	Neonates	Mean 4.97 (3.31) yr (survivors); 4.92 (3.87) yr (non-survivors)
Choi 2017	NR	Retrospective cohort	Korea	1	2012	2015	PICU of unknown composition	Chart review	83	Consecutive	Infants	Mean 128 (159.6) mo
Couto-Alves 2013	Govt.	Retrospective cohort	United Kingdom, Austria and Holland	6	1996	2011	PICU of unknown composition	Prospective data collection	309 development, 623 validation, 134 replication	NR/Unable to determine	Children	Mean 5.12 (0.3) yr
da Silva 2008	NR	Retrospective cohort	Brazil	1	1998	2001	Other Oncologic PICU	Chart review	196	Consecutive	Infants	Mean 8.4 (5.4) yr
Fijnvandraat 1995	NR	Case series	The Netherlands	1	1990	1992	PICU of unknown composition	Prospective data collection	35	Consecutive	Children	Median 4.3 [0.13-15] yr
Gonzalez-Vicent 2005	Other: Fundacion Oncohematologia Pediatrica	Retrospective cohort	Spain	1	1998	2002	PICU of unknown composition Hospital floor outside the ICU	Chart review	198	Consecutive	Adolescents	Median 7 [1-18] yr
Hu 2017	Govt.	Case/control study	China	1	2010	2016	Emergency room	NR/Unable to determine	296 for derivation and 68 for validation	Consecutive	Children	Mean 7.8 (3.13) yr in non-PHI group and 8.19 (3.28) yr in PHI group
Jhang 2016	NR	Other retrospective observational	Korea	1	2013	2014	Mixed PICU	Chart review	191	Consecutive	Infants Children Adolescents	Mean 29 mo [2-215]

Kornelisse 1997	NR	Prospective cohort	Netherlands	1	1988	1995	PICU of unknown composition	Chart review Prospective data collection	75	Consecutive	NR/Unable to determine	Median 3.2 y (3 weeks-17.9 y)
Leteurtre 2001	NR	Prospective cohort	France	1	1993	2000	PICU of unknown composition	Prospective data collection	58	Consecutive	Neonates	Median 24 mo [IQR 12-44 mo]
Malley 1996	NR	Retrospective cohort	USA	3	1985	1994	NR/Unable to determine	Chart review	245	Other	Infants	Median 24 mo [0.7-228 mo]
Martins 2015	NR	Retrospective cohort	Portugal	1	2000	2013	NR/Unable to determine	Chart review Other unit database	76	Consecutive	Children	'all children'
Meyer 2005	NR	Retrospective cohort	Germany	1	2001	2003	PICU of unknown composition	Chart review	32	Consecutive	Children	Median 11.5 y, range 1 mo-22 y
Peters 2001	NR	Prospective cohort	United Kingdom	3	1993	1999	PICU (non-cardiac only)	Chart review Prospective data collection	32 in derivation set; 195 in validation set	Consecutive	Infants, Children	Survivors (n = 26): Median 2y [IQR: 1y – 5y] NS (n=6): Median 0 y [IQR: 0y – 2.5y]
Silva 2007	NR	Retrospective cohort	Brazil	2	2000	2005	PICU of unknown composition	Chart review	72	NR/Unable to determine	Infants, children	Range 2 - 156 mo Survivors (n = 54): Median 33 [IQR: 14 – 60] mo NS (n = 14): Median 28 [IQR: 9 – 48] mo
Ramby 2015	Govt.	Retrospective cohort	USA	1	2009	2010	PICU of unknown composition	Chart review	596	Consecutive	Not reported	Median 4.4 [IQR: 1.5 – 12.9] yr
Li 2019	none	Prospective cohort	China	1	2015	2018	PICU of unknown composition	Chart review Prospective data collection	404	NR/unable to determine	Children, adolescents	Median 12 mo [IQR: 4 – 60 mo]
Said 2017	Govt.	Retrospective cohort	USA	1	2005	2012	Mixed PICU	Chart review	3913	Consecutive	Not reported	Mean 7.45 (6.7) yr
Kim 2019	Govt.	Retrospective cohort	Korea	1	2009	2017	PICU of unknown composition	Chart review	101	Consecutive	Unable to determine	Median 13 [IQR: 8 - 16] yr
Niederwanger 2018	none	Retrospective cohort	Austria	1	2000	2014	PICU of unknown composition	Chart review	250	Consecutive	Neonates, Infants, Children, Adolescents	Median 35 [IQR: 6 – 109] mo

Ye 2018	Govt.	Retrospective cohort	China	1	2014	2016	PICU of unknown composition	Chart review	4723	Consecutive	Infants, Children, Adolescents	Mean 3.3 (3.8) yr
Nam 2018	Govt.	Retrospective cohort	Korea	1	2016	2016	PICU of unknown composition	Chart review	232	Consecutive	Not reported	Mean 7.2 (5.9) yr (control, N=201); mean 7.9 (7.1) yr (SIRS, N=25); mean 10.8 (5.6) yr (sepsis, N=6)
Jain 2018	Not reported	Prospective cohort	India	1	2014	2015	PICU of unknown composition	Chart review	141	Consecutive	Children	Mean 19.5 (18.3) mo
Kalkwarf 2018	Not reported	Retrospective cohort	USA	1	2010	2016	Trauma center	Chart review	1292	Consecutive	Infants, Children, Adolescents	Median 14 [IQR: 6-16] yr (survivors, N=1169); Median 11 [IQR: 4-16] yr (NS, N = 123)
Sachdev 2018	None	Retrospective cohort	India	1			PICU of unknown composition	Chart review	101	Consecutive	Infants, Children, Adolescents	Median (range): 72 (4-196) mo (NS, N=11); Median (range) 36 (1.5 – 196) mo (Survivors, n = 90)
Purbiya 2018	None	Retrospective cohort	India	1	2014	2015	PICU of unknown composition	Chart review	209	Consecutive	Children	NR

Abbreviations: Govt., government; NGO, nongovernmental organization; NR, NR; PICU, pediatric intensive care unit; PCICU, pediatric cardiac intensive care unit; IQR, interquartile range; SD, standard deviation; wks, weeks; 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)

Supplemental Table 2. Performance Characteristics for Assessment Tools and Scores for Hematologic Dysfunction in Critically Ill Children (n=29 studies)

Source Year	Score/ assessment tool	Inclusion criteria	Timing of score/tool assessment	Outcomes	Performance characteristics
An 2016	Pediatric Critical Illness Score	HSCT patients	pre-HSCT and day 1 of PICU	Mortality	Reports p value for multivariable analysis of 0.04 for pediatric critical illness score. Unadjusted OR 4.2 (1.3, 13.79) for every 10-point decrease in PCIS below a PCIS of 90
Bestati 2010	Blood cell counts PELOD score	Unable to determine PICU characteristics	first 7 days of PICU	Mortality	AUROC: day 1 PELOD AUROC for mortality 0.78 in neonates; day 1 PELOD AUROC for mortality 0.93 Other: OR for hematological portion of PELOD (mortality) for neonates 1.6 (0.96, 2.69); OR for mortality for hematologic portion of PELOD for older children 1.16 (1.09, 1.312)
Castellanos-Ortega 2002	Blood cell counts Meningococcal septic shock prognostic score	PICU patients with meningococcal septic shock		Mortality	AUROC: AUROC for meningococcal score: 0.91 (derivation cohort) 0.88 (validation cohort) aOR: for leukocyte count less than 4,000 1.55 (95% CI 1.1, 2.2) Goodness of fit: Hosmer Lemeshow p value for meningococcal score: 0.55 (derivation cohort) 0.47 (validation cohort)
Chhangani 2015	APACHE II score	Unable to determine PICU characteristics	PICU day 1	Mortality	APACHE II: AUROC: 0.889 (0.85, 0.93) Goodness of fit: Hosmer-Lemeshow p = 0.726 Other: WBC 15869.98 +/- 7537 survivors vs. 20307.18+/-9036.4 nonsurvivors on univariate analysis, p=0.009 Hematocrit not significantly different between survivors and nonsurvivors
Choi 2017	Blood cell counts	General PICU population (mixed cardiac and non-cardiac)	within 1 hour of PICU admission	Mortality	Se: 71.4 (platelet count < 52,000, all patients); 78.6 (platelet count < 30.5, patients with hematologic oncologic diagnosis); 85.7 (platelet count < 106.5, patients without hematologic oncologic diagnosis) Sp: 71 (platelet count < 52,000); 66.7 (platelets < 30.5, patients with hematologic oncologic diagnosis); 78.9 (platelets < 106.5, patients without hematologic oncologic diagnosis) PPV: 45.5 (platelets < 52,000, all patients); 57.9 (platelets < 30.5, patients with hematologic oncologic dx); 42.9 (platelets< 106.5, patients without hematologic oncologic diagnosis) NPV: 88 (platelets < 52, all patients); 84.2 (platelets < 30.5, patients with hematologic oncologic diagnosis); 96.8 (platelets < 106.5, patients without hematologic oncologic diagnosis) LR: 6.11 (all pts); 7.33 (pts with hematologic oncologic diagnosis); 22.5 (pts without hematologic oncologic diagnosis AUROC: platelet count to predict mortality: 0.8 (95% CI 0.69, 0.9) for all subjects; 0.722 (0.55, 0.9) for patients without hematologic oncologic diagnosis; 0.86 (0.7, 1) for patients with hematologic oncologic diagnosis (n = 38) aOR: 0.988 (95% CI: 0.977, 0.999)
Couto-Alves 2013	Blood cell counts Other INR, aPTT, fibrinogen, platelet	General PICU population (mixed cardiac and non-cardiac)	lab data from 'the first recorded sample'	Mortality	BEP score (Model constructed by platelet count and base excess) to predict mortality: AUROC: 0.86 (95%CI: 0.8, 0.91)
da Silva 2008	Blood cell counts Other	Oncology patients	Initial values	Mortality	Adjusted HR for initial granulocyte count 1.3 (0.7, 2.7); aHR for duration of granulocytopenia: 2.4 (1.2, 4.9)

	initial granulocyte count and duration of granulocytopenia				Variables included in multivariable model to predict mortality: Number of organ dysfunctions (aHR 7.4, p<0.0001), respiratory infection (aHR 2.3; p=0.005), duration of granulocytopenia (aHR 2.4, p=0.02)), Initial granulocyte count (aHR 1.3, p=0.4), Underlying disease (aHR 0.8, p=0.4). chi square statistic for model: 51.122, p <0.0001
Fijnvandraat 1995	Blood cell counts Other coagulation tests and GMPS score	General PICU population (only non-cardiac)	within 2 hours of PICU admission	Mortality	Mean (SD) platelet count 128 (73) in survivors vs. 65 (61) x 10^9/l in non-survivors
Gonzalez-Vicent 2005	Other 'score of PICU admission'	HSCT patients	During HSCT procedure	Mortality Other PICU admission	Kaplan-Meier (for probability of ICU admission) high risk: 63.8 +/- 8.8 v. low risk: 8.8 +/- 2.2%; log rank p < 0.0001 Autologous transplant, lower O-PRISM score, lower CRP, lack of multiorgan failure, lack of inotropic drug associated with higher event-free survival on univariate analyses.
Hu 2017	Blood cell counts Coagulation assays	Other ED patients with TBI	On arrival to ED & initial head CT on arrival	progressive hemorrhagic intracranial hemorrhage	C-statistic 0.873 (p=0.586) for derivation and Hosmer-Lemeshow tests 0.877 (p=0.524) for validation Model to predict progressive hemorrhagic brain injury includes: GCS score, intra-axial bleeding/brain contusion, midline shift, platelet count < 100,000 (aOR 7.86 [2.3, 26.4]), PATIENTS> 14s (aOR 3.1[1.6, 6.2]), INR > 1.25 (aOR 3.92 [1.8, 8.8]), D-dimer >=5 (aOR 9.9 [3.1, 32.2]), hyperglycemia
Jhang 2016	Blood cell counts ISTH and JAAM DIC scores	General PICU population (mixed cardiac and non-cardiac) Oncology patients HSCT patients	Day 1 of PICU admission	Mortality	AUROC: 0.788 for JAAM DIC score and 0.72 for ISTH DIC score JAAM DIC score: >= 3 SIRS criteria (1 point) Platelet count 80 – 120 or 30% decrease within 24 hr (1 point) or < 80 or 50% decrease within 24 hrs (3 points) Prothrombin time (patient / normal value) < 1.2 (1 points) or >= 1.2 (3 points) Fibrinogen degradation product (mg/dL) 10 – 25 (1 point) or >=25 (3 pointts) ISTH DIC score: Platelet count 50- 100 (1 point) or < 50 (2 points) D-dimer 1-5 micrograms/mL (2 points) or > 5 (3 points) Fibrinogen <= 100 dg/L (1 points) Prothrombin time (s) 3 - 6 (1 point) or > 6 (2 points)
Kornelisse 1997	Blood cell counts Rotterdam score	General PICU population (mixed cardiac and non-cardiac)	Day 1	Mortality, amputation, skin grafting, neurologic	PPV: 86% for Rotterdam score Score includes: CRP, serum potassium, base excess, and platelet count)
Leteurtre 2001	Blood cell counts	Septic shock with purpura (SSP)	Day 1	Mortality	AUROC: PRISM best at 0.95; other scores also reported
Malley 1996	Blood cell counts Other perfusion Model 1/ fibrinogen Model 2	Invasive meningococcal disease	First values obtained	death, amputation, or loss of all 5 digits on one extremity	Se: 82% model 1, 89% model 2 Sp: 97% model 1, 97% model 2 PPV: 87% model 1, 89% model 2 NPV: 97% model 1, 97% model 2 AUROC: no values given Model 1: ANC < 3,000, poor perfusion, Platelet count < 150 Model 2: Fibrinogen < 250, ANC < 3,000

Martins 2015	Blood cell counts Base excess (BEP score) Base excess x platelet count	Invasive meningococcal disease	Day 1	Mortality, Categories of organ dysfunction in survivors vs. non-survivors	Base excess and platelet count score (BEP score) AUROC: 0.81 (95% CI: 0.66 – 0.97) For cutoff of 0.06: Se: 83 Sp: 83 PRISM: AUROC 0.96 (0.91 - 1) Hematological organ failure (not defined) associated with mortality aOR 11.7 (1.4, 96.1)
Meyer 2005	Risk score for pediatric cancer patients admitted to the ICU	Oncology patients HSCT patients	Within 2 hours of PICU admission	Mortality	For a risk score cutoff value of >3 points: Se: 100% (CI: 65, 100) Sp: 92% (CI: 74, 99) PPV: 100% (CI: 86, 100) NPV: 78% (CI: 40, 97) Factors included in the risk score: non-solid tumor, > 2 organ failures, neutropenia, septic shock, mechanical ventilation, and inotropic medication
Peters 2001	Blood cell counts	Clinical meningococcal disease	first obtained values	Mortality	Se: 73% for platelets x ANC product < 40 Sp: 99% for platelets x ANC product < 40 PPV: 82% for platelets x ANC product < 40 AUROC: 0.97
Silva 2007	Blood cell counts	PICU patients with meningococcal disease	first platelet and neutrophil counts obtained	death, amputations of limbs or digits, CNS bleed	Se: 28.6 (8.6-58.1) with PN </= 113 Sp: 96.6 (88-99) with PN </= 113 PPV: 66.7 with PN </= 113 NPV: 84.8 with PN </= 113 AUROC: 0.85 (0.74-0.92) with PN </= 113
Ramby 2015	Red cell distribution width	All patients admitted to PICU	First 24 hours	PICU LOS > 48 hours; PICU Mortality	PICU LOS > 48 hours: aOR for sepsis patients 0.91 (0.73, 1.13) aOR for non-sepsis patients 1.17 (1.06, 1.3) AUROC 0.61 PICU mortality: aOR 1.2 (1.07, 1.35 AUROC 0.65 (0.55, 0.75) PIM-2 AUROC 0.75 (0.66, 0.83) PIM-2 + RDW AUROC 0.78 (0.7, 0.86) Optimum cut-point for mortality: >= 14.5 Se 69% (52, 83); Sp 54% (50, 59); PPV 10% (6, 14); NPV 96% (93, 98) Using multiple cut points for mortality: < 13.4 (low risk) and > 15.7% (high risk): NPV 96.7%, PPV 12.9%
Li 2019	Red cell distribution width	Non-cardiac admitted to PICU.	First 24 hours	PICU mortality	aOR 1.79 (0.984, 2.61) AUROC 0.72 (0.68, 0.77) RDW >= 15.5 (optimum cut point): Se 75.8 (66.1, 83.8) Sp 63.6 (57.9, 69) PPV 40.4% (33.2, 47.7) NPV 89% (84.1, 92.8)
Said 2017	Red cell distribution width	General PICU population (mixed cardiac and non-cardiac)	First CBC in first 24 hours	PICU mortality or ECMO	AUROC 0.611 AUROC for PIM-2: 0.901 AUROC for combined PIM-2 and RDW: 0.904 aOR, controlling for PIM-2, 1.127

Kim 2019	Hematocrit; pSOFA, PELOD	Oncology patients	Day 1	Mortality	Hematocrit: aOR 0.86 (0.76, 0.96) pSOFA: AUROC (95%CI) 0.8 (0.72, 0.88) PELOD: AUROC (95% CI) 0.76 (0.67, 0.84
Nam 2018	Combined delta neutrophil index and mean platelet volume	Other Unable to determine PICU characteristics	Not reported	Mortality, Sepsis	Sepsis: delta neutrophil% AUC 0.97; neutrophil distribution width AUC 0.79; monocyte distribution width AUC 0.77; platelet count AUC 0.79; mean platelet volume AUC 0.66; plateletcrit AUC 0.79; immature platelet fraction AUC 0.77 Mortality: WBC count HR 9.12 (2.8,29.6); delta neutrophil% HR 19 (2.4, 151); neutrophil distribution width HR 15 (3.3, 70); monocyte distribution width HR 1.3 (1.2, 1.5); platelet count HR 1.56 (0.46, 5.24); mean platelet volume HR 14 (1.7, 113); immature platelet fraction HR 12 (1.5, 97); delta neutrophil% plus mean platelet volume AUC 0.99
Niederwanger 2018	Blood Cell Counts	Sepsis	Day of peak level of CRP	Mortality	Platelet count: aOR for survival: 1.94 (1.3, 3.3) per 50,000
Ye 2018	Platelet volume indices and red cell distribution width	Children on mechanical ventilation	Not reported	PICU mortality	For children > 3 years of age: Univariate analysis: Platelet count 292 +/- 102 (survivors) vs 193 +/- 129 (NS) p < 0.001 Platelet count: aOR 1.01 (1, 1.01) on multivariable analysis Longitudinal MPV over the first week of ICU admission, non-survivors appear to have decrease in MPV over the first 72 hours followed by increase Univariate analyses: PDW 58 +/- 23 (survivors) vs. 48 +/- 25 (nonsurvivors), p 0.01 (not significant on multivariable analysis); RDW 13.2+/- 1.7 (survivors) vs 14.1 +/- 2.2 (nonsurvivors) p<0.001 (multivariable analysis nonsignificant) For infants and children < 3 years of age: Univariate analysis: Platelets count 340.6 +/- 147 (survivors) vs 319.6 +/- 168 (NS) p<0.001; No significant difference in PDW between survivors and nonsurvivors; RDW 14.5 +/- 2.5 (survivors) vs 13.9 +/- 2 (NS) p < 0.001
Jain 2018	Blood cell counts	Severe community acquired pneumonia	Hospital admission	mortality	Platelet count < 70,000 aOR 10.7 (1.3, 78.7)
Kalkwarf 2018	Blood cell counts	Severe trauma	Admission	mortality	Platelet count: < 30,000 100% PPV; 92% NPV, Se 1%, Sp 100% < 40,000 67% PPV, 92% NPV, Se 2%, Sp 99% < 50,000 60% PPV, 92%NPV, Se 3%, Sp 99% < 60,000 33% PPV, 92% NPV, Se 3%, Sp 99% < 70,000 40%PVV, 92%NPV, Se 4%, Sp 99% Hb < 5: 100% PPV, 92% NPV
Sachdev 2018	Red cell distribution width	PICU patients	Admission	Hospital mortality	Day 1 RDW: 15.7 – 18.04, aOR 1.05 (0.95, 1.16) 18.04 – 21.5 aOR 1.26 (1, 1.59) <= 21.5 aOR 1.4 (1.06, 1.83)

Abbreviations: aOR, adjusted odds ratio; AUROC, area under the receiver operating characteristics curve; HR, Hazard Ratio; KM, Kaplan Meier curve; LR, Likelihood Ratio; MV, multivariable; PPV, positive predictive value; NPV, negative predictive value; Se - sensitivity; Sp, specificity; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; BiPAP, Bilevel positive airway pressure; BNP, brain natriuretic peptide; CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; CK, creatine kinase; CO, cardiac output; CPAP, continuous positive airway pressure; CPR, cardiopulmonary resuscitation; CRP, C-reactive protein; CRT, capillary refill time; DCM, dilated cardiomyopathy; ECG, electrocardiogram; Echo, Echocardiogram; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; HIE, Hypoxic ischemic encephalopathy; ISS, severity of injury score; LR, likelihood ratio; LV, left ventricle; LSI, life-saving intervention; MCS, mechanical circulatory support; mins, minutes; mo, months; MPI, myocardial performance index (Tei Index); NIRS, near infrared spectroscopy; NYHA, New York Heart Association; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; PCICU, pediatric cardiac intensive care unit; PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality score; RV, right ventricle; SD/DD - systole to diastole duration; Se, sensitivity; SI, shock index; SIPA, age adjusted shock index; Sp, specificity; yr, years

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Research Priorities

1. What thresholds of cytopenia are most predictive of adverse outcomes in critically ill children?

2. Should the definition of hematologic dysfunction include the cause(s) of cytopenias, with “marrow failure” defined as cytopenias resulting from decreases in cellular production compared to normal values and “insufficient compensatory production” defined as cytopenias resulting from increased destruction or utilization of a cell type?

3. Should the definition of hematologic dysfunction include abnormal function in addition to abnormal quantity of cells/cellular components?