Coagulation Dysfunction Criteria in Critically Ill Children:

The PODIUM Consensus Conference

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Data Supplement

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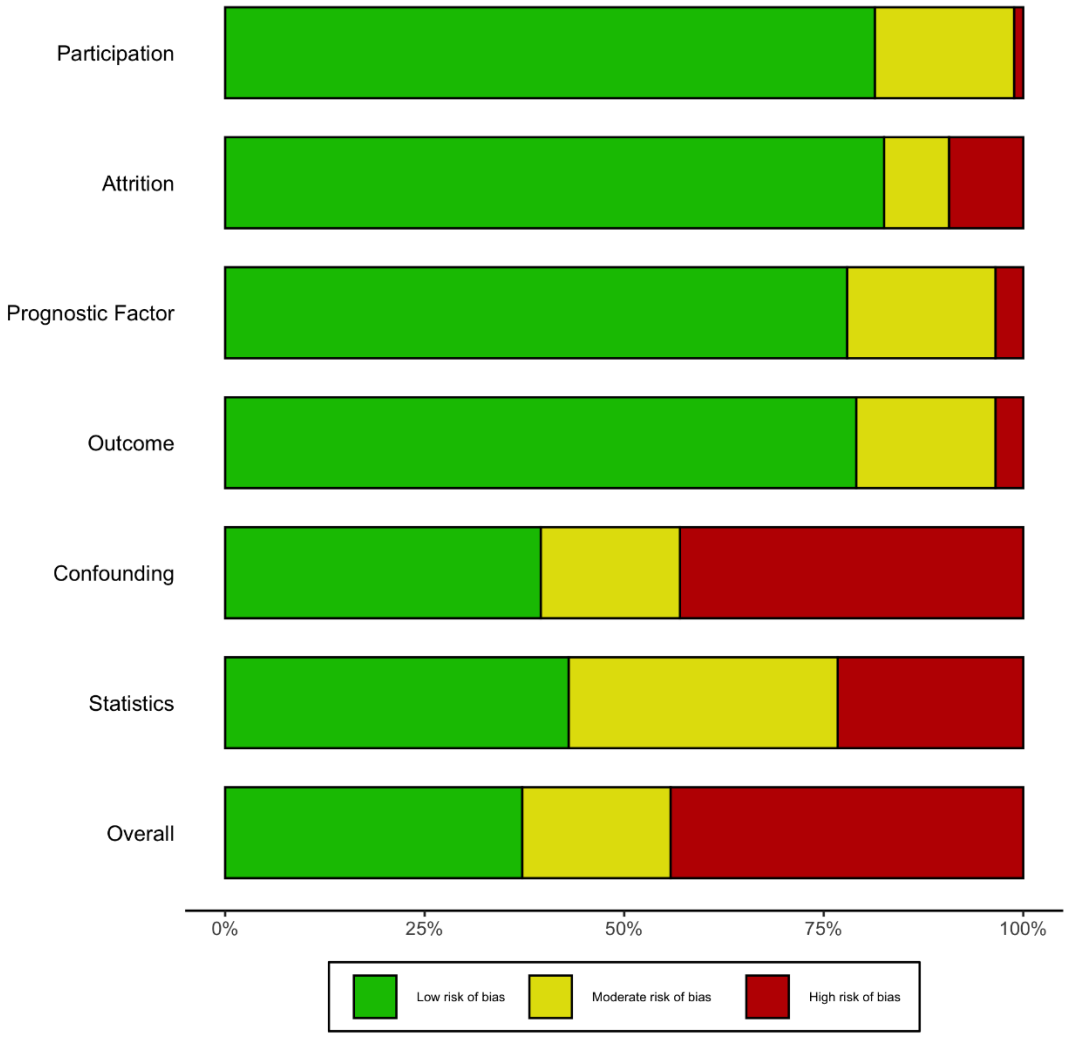

Supplemental Table 1. Studies Included in the PODIUM Coagulation Dysfunction Systematic Review (n=86 studies)

Author (yr)	Funding	Study design	Location	No. of sites	Study years	Setting	Data source(s)	Sample size	Recruitment	Age categories[a]	Age details
A – Platelets											
Baslaim 2006	NR	Retrospective cohort	Saudi Arabia	1	2000-2004	PCICU (cardiac only)	Chart review	26	Consecutive	Neonates Infants Children	Mean 16.4 mo [range 0.5-144]
ElBassetAboElEzz 2017	NR	Prospective cohort	Egypt	1	2014-2015	PICU of unknown composition	Prospective data collection	40	NR/Unable to determine	Children Adolescents	Age of patient group ranged from 1.5 to 8.5 yr with mean age of 4.9
Faraoni 2015	NGO	Retrospective cohort	Belgium	1	2010-2012	PCICU (cardiac only)	Registry	150	Consecutive	Infants Children	Median 14 mo [5-40]
Jhang 2018	NR	Retrospective cohort	South Korea	1	2013-2017	PICU (non-cardiac only)	Chart review	89	Consecutive	Neonates Infants Children Adolescents	Median 117.3 mo [range 0-286.4]
Leeper 2017	NR	Prospective cohort Observational/ descriptive study	USA	1	2015-2016	Emergency room (ER)	Prospective data collection	133	Consecutive	Infants Children Adolescents	Median 10 yr [IQR 5-13]
Leeper 2018	NGO	Prospective cohort Observational/ descriptive study	USA	1	2015-2017	PICU (non-cardiac only)	Prospective data collection	101	Consecutive	Infants Children Adolescents	Median 8 yr [IQR 4-12]
Lin 2017	NGO	Prospective cohort Observational/ descriptive study	Taiwan	1	2012-2015	PICU of unknown composition	Prospective data collection	42	Consecutive	Infants Children	Median 4.1 yr [IQR 1.7-8.7]
Liras 2015	NR	Retrospective cohort	USA	1	2010-2013	Emergency room (ER)	Registry	1819	Consecutive	Children Adolescents	Hyperfibrinolytic group median 11 yr [IQR 4-15], non hyperfibrinolytic group median 15 yr [IQR 9-16] p<0.001
Liras 2017	NR	Retrospective cohort	USA	1	2010-2016	Emergency room (ER),NR/Unable to determine	Registry	956	Consecutive	NR/Unable to determine	Coagulopathic group median 14 yr [IQR 6-16], control group median 15 yr [IQR 9-16], p=0.008
Moxon 2015	NR	Prospective cohort	Malawi	1	2008-2011	NR/Unable to determine	Chart review Prospective data collection	malaria patients =267; controls =135	NR/Unable to determine	NR/Unable to determine	Retinopathy (+) malaria: median 45 mo (95%CI 33-62); retinopathy (-) malaria: 45 mo (95%CI 28-52)
Oladunjoye 2018	NR	Prospective cohort	USA	1	2015-2016	PCICU (cardiac only)	Prospective data collection	202	Consecutive	Neonates Infants Children	Median age at surgery 0.4 yr [IQR 0.1-2.3]

Padungmaneesub 2019	NGO	Prospective cohort	Thailand	1	2016-2016	Mixed PICU (cardiac and non-cardiac)	Prospective data collection	103	Consecutive	Infants Children Adolescents	Mean 3.6 yr (4.4)
Rajkumar 2017	NR	Prospective cohort Observational/ descriptive study	India	1	2015-2016	NR/Unable to determine	Prospective data collection	87	NR/Unable to determine	Infants Children	Range 6 mo-14 yr
Rajpurkar 2019	Govt.	Non-randomized/quasi randomized controlled trial	NR	NR	Other (oncology units)	Prospective data collection	79	Consecutive	Children Adolescents	NR	NR
Schmidt 2018	Industry	Randomized controlled trial (RCT) cross-over RCT pragmatic RCT	USA	1	NR	NR/Unable to determine	Prospective data collection	162	Consecutive	Neonates Infants Children Adolescents	Median 7 mo [range 2 days - 17 yr]
Schneider 2011	NR	Prospective cohort	France	1	NR	PICU of unknown composition	Chart review Prospective data collection	49 (25 control; 24 patients)	NR/Unable to determine	Children Adolescents	Median 9.7 yr [range 2-17]
Schochl 2011	NR	Retrospective cohort	Austria	1	2005-2010	NR/Unable to determine	Chart review Prospective data collection	88	NR/Unable to determine	Adolescents	Mean 48yr [range 13-87]
Selim 2005	NR	Prospective cohort	Egypt	1	NR	Other (NICU)	Prospective data collection	33	NR/Unable to determine	Neonates	NR
Selladurai 1997	NR	Retrospective cohort Case series (patients compiled in serial fashion lacking a control group)	Malaysia	1	NR	NR/Unable to determine	Chart review Prospective data collection	204	NR/Unable to determine	NR/Unable to determine	NR
Thebaud 1999	NR	Case series (patients compiled in serial fashion lacking a control group)	France	1	1986-1994	PICU of unknown composition	Chart review Prospective data collection	14	Consecutive	Infants Children	Range 2-33 mo
Tzanetos 2012	Govt.	Prospective cohort Case series (patients compiled in serial fashion lacking a control group)	USA	1	NR	PCICU (cardiac only)	Prospective data collection	16	Consecutive	Neonates Infants Children	+ thrombus (n=5): mean 196.8 days (368.7); no thrombus (n=11): mean 518.7 days (436.2)
Vogel 2013	NR	Retrospective cohort Case series (patients	USA	1	2009-2011	Mixed PICU (cardiac and non-cardiac)	Chart review Prospective data collection Registry	86	Consecutive	Children Adolescents	Median 8yr (all</=14yr of age) [IQR 3, 12]

		compiled in serial fashion lacking a control group)									
Zavadil 1998	NR	Retrospective cohort	USA	1	1992-1997	NR/Unable to determine	Chart review Prospective data collection	30	Consecutive	Neonates	Hemorrhage group (n=13): mean 46.7 hours (75.5); non-hemorrhage cohort (n=17): mean 39.1 hours (70.0) (cohorts defined by amount of transfusions received)
Zinter 2016	NR	Prospective cohort	USA	5	2008-2014	Mixed PICU (cardiac and non-cardiac)	Prospective data collection	259	Consecutive	Infants Children Adolescents	Median 5.2 yr [IQR 1.1-13.2]
Zubair 2015	NR	Retrospective cohort Observational/ descriptive study	USA	1	2008-2014	Other (pre-op testing)	Chart review Prospective data collection	402	NR/Unable to determine	Infants Children	Median 2.3 yr [IQR 0.5-9.3]
B - INR											
Algren 1993	NR	Prospective cohort	USA	1	1988-1991	PICU of unknown composition	Chart review Prospective data collection		Consecutive	Infants Children Adolescents	Mean 3 yr, median 1 yr [range 3mo-16 yr]
Borgman 2011	NR	Retrospective cohort	Iraq Afghanistan Germany	145	2002-2009	Other (military treatment centers and German hospitals unspecified if ICU)	Registry	1101	Consecutive	Children Adolescents	Median 15 yr [IQR 10-16]
Cheuk 2004	NR	Retrospective cohort	Hong Kong	1	1992-2002	PICU of unknown composition	Chart review EMR query	19	Consecutive	Neonates Infants Children Adolescents	Median 7.8 yr [range 8 mo-17 yr]
Grandjean-Blanchet 2018	NR	Retrospective cohort	Canada	1	2008-2016	Emergency room (ER)	Chart review	284	Consecutive	NR/Unable to determine	
Hu 2017	Govt.	Case/control study (case matched) Retrospective cohort	China	1	2010-2016	NR/Unable to determine	Chart review	derivation cohort= 296; validation cohort= 68	NR/Unable to determine	Children Adolescents	Mean 8 yr (3 yr)
Lal 2011	NR	Prospective cohort Observational/ descriptive study	India	1	2007-2009	Hospital floor outside the ICU	Prospective data collection	31	Consecutive	Children Adolescents	Mean 8.77 yr (3.62)
Leeper 2015	NR	Retrospective cohort	USA	1	2005-2014	NR/Unable to determine	Chart review Registry	101	Consecutive	Infants Children	Median 2 mo [IQR 1-12]

Leeper 2016	NR	Retrospective cohort Observational/ descriptive study	USA	1	2005-2014	PICU of unknown composition	Registry	776	Consecutive	Neonates Infants Children Adolescents	Mean 8.4 yr (5.5)
Leeper 2016	NR	Retrospective cohort Observational/ descriptive study	USA	1	2005-2014	NR/Unable to determine	Registry	101	Consecutive	Neonates Infants	INR >1.3 group: median 3 mo [1 mo - 2 y]; INR <1.3 group: median 2 mo [1 mo to 1 y]
Liu 2006	Govt.	Retrospective cohort	USA	1	1993-2003	NR/Unable to determine	Registry	81	Consecutive	Neonates Infants Children Adolescents	Mean 6.8 yr (6.5), median 4.5 yr [IQR 0.7-12.8]
Lu 2008	Govt.	Retrospective cohort	USA	1	2002-2006	NR/Unable to determine	Registry	53	Consecutive	Neonates Infants Children Adolescents	Median 3.6 yr [range 0-17.1]
Lu 2013	NR	Prospective cohort	USA UK Canada	24	1999-2008	Other (hospitalized children)	Prospective data collection	579	Consecutive	Neonates Infants Children Adolescents	Median 5.5 yr [IQR 1.1-13.5]
McDiarmid 2002	NGO	Retrospective cohort	USA Canada	29	NR	NR/Unable to determine	Registry	884 (death); 779 (death or move to ICU)	NR/Unable to determine	NR/Unable to determine	NR
Patregnani 2012	NR	Retrospective cohort Observational/ descriptive study	USA Germany (US Military)	7	2002-2009	Other (military theater hospital trauma registry)	EMR query	744	NR/Unable to determine	Children Adolescents	Median 9 yr [IQR 5-12]
Podolsky-Gondim 2018	NR	Retrospective cohort	Brazil	1	2013-2016	PICU (non-cardiac only),Hospital floor outside the ICU	Chart review	66	Consecutive	Infants Children Adolescents	Mean 10.9 yr [range 3 mo - 17 yr]
Ranucci 2019	NGO Industry	Secondary analysis of RCTs including subgroup analysis Prospective cohort	Italy	1	NR	PCICU (cardiac only),Operating room (OR)	Prospective data collection	77	Other (some patients enrolled in a previous RCT reported in 2017, the remaining 20 enrolled as a prospective cohort in 2017-2018)	Infants	Median 6 mo [IQR 2-6]
Srivastava 2012	NR	Retrospective cohort Case series (patients	India	1	2000-2008	PICU of unknown composition	Chart review	130	NR/Unable to determine	NR/Unable to determine	Mean 7.5 yr (4.5)

		compiled in serial fashion lacking a control group)									
TudeMelo 2010	NGO	Retrospective cohort Case series (patients compiled in serial fashion lacking a control group) Cross-sectional study	France	1	NR	Mixed PICU (cardiac and non-cardiac)	Chart review Prospective data collection	315	Consecutive	Infants Children Adolescents	Median 77 mo [range 1m-17y]
Yang 2019	Govt.	Retrospective cohort	China	1	2007-2018	PCICU (cardiac only)	Chart review	56	Consecutive	Infants Children	Median 39 mo [range 1.5, 103.5]
C - Fibrinogen											
Couto-Alves 2013	Govt.	Retrospective cohort	UK Austria Holland	6	1996-2011	PICU of unknown composition	Prospective data collection Registry	1073	Consecutive	Neonates Infants Children Adolescents	Mean 5.12 yr (0.3)
Ersoy 2007	NR	Prospective cohort	Turkey	1	NR	NR/Unable to determine	Prospective data collection	58	NR/Unable to determine	Neonates	Cases of culture positive sepsis: mean 5.8 (4.5) days, culture negative controls mean 7.5 (4.6) days, p>0.05
Faraoni 2014	NGO	Retrospective cohort	Belgium	1	2010-2012	PICU of unknown composition, Operating room (OR)	Registry	156	Consecutive	Infants Children	Bleeding group: median 4.3 mo [1.8,13]; nonbleeding group: median 15.7 mo [6.8,45]
Graciano 2005	NR	Prospective cohort Observational/ descriptive study	USA	1	1996-1999	Mixed PICU (cardiac and non-cardiac)	Chart review	6456	Consecutive	Children NR/Unable to determine	Mean 4.6 yr (5.3)
Huang 2011	NR	Retrospective cohort	Taiwan	1	2000-2009	NR/Unable to determine	Chart review Prospective data collection	109	NR/Unable to determine	Neonates Infants Children Adolescents	Mean 5.8 yr
Jevtic 2010	NR	Prospective cohort	Serbia	1	2004-2009	Mixed PICU (cardiac and non-cardiac)	Prospective data collection	74	Consecutive	Infants Children Adolescents	Range 3 mo - 195 mo
Malley 1996	NR	Retrospective cohort	USA	2	1985-1990	NR/Unable to determine	Chart review	153	Consecutive	Infants Children Adolescents	Median 24 mo [range 0.7-228]
McManus 1993	NR	Retrospective cohort	USA	1	1982-1992	Mixed PICU (cardiac and non-cardiac)	Chart review	53	NR/Unable to determine	Neonates Infants Children	Median 4.9 yr [range 18 days-17 y]
Mitra 2017	NR	Prospective cohort	India	1	NR	NR/Unable to determine	Chart review Prospective data collection	65	NR/Unable to determine	Neonates	NR

Niederwanger 2018	None	Case series (patients compiled in serial fashion lacking a control group)	Austria	1	2000-2014	PICU (non-cardiac only)	Chart review	250	Consecutive	Neonates Infants Children Adolescents	Median 35 mo [IQR 6-109]
Podolsky-Gondim 2018	NR	Retrospective cohort	Brazil	1	2013-2016	PICU (non-cardiac only),Hospital floor outside the ICU	Chart review	66	Consecutive	Infants Children Adolescents	Mean 10.9 yr [range 3 mo - 17 yr]
Ranucci 2019	NGO Industry	Secondary analysis of RCTs including subgroup analysis Prospective cohort	Italy	1	NR	PCICU (cardiac only),Operating room (OR)	Prospective data collection	77	Other (some patients enrolled in a previous RCT reported in 2017, the remaining 20 enrolled as a prospective cohort in 2017-2018)	Infants	Median 6 mo [IQR 2-6]
Tirosh-Wagner 2011	NR	Prospective cohort Case series (patients compiled in serial fashion lacking a control group)	Israel	1	NR	Mixed PICU (cardiac and non-cardiac),NR/Unable to determine	Chart review Prospective data collection	15	NR/Unable to determine	Infants Children	Mean 28 mo [range 1 mo-10 yr]
D – D-dimer											
Chen 2017	Govt.	Retrospective cohort	China	1	2012-2014	PICU of unknown composition	Chart review	788	Consecutive	Infants Children	Median 8.5 mo [IQR 3.0-20.0]
Foaud 2014	NR	Case/control study (case matched) Prospective cohort Observational/descriptive study	Egypt	1	2012-2013	PICU of unknown composition	Prospective data collection	66	Consecutive	Children Adolescents	Mean cases of TBI 6.9 yr (3.8); healthy controls 6.8 yr (2.3)
Oren 2005	NR	Retrospective cohort	Turkey	1	1988-2003	Hospital floor outside the ICU	Chart review	62	NR/Unable to determine	Infants Children Adolescents	Mean 4yr (range 2 mo-17 yr)
Qi 2014	NR	Case/control study (case matched) Prospective cohort	China	1	NR	PICU of unknown composition	Prospective data collection	67	NR/Unable to determine	NR/Unable to determine	NR

Wang 2012	NR	Prospective cohort Case series (patients compiled in serial fashion lacking a control group)	China	1	2010-2011	Mixed PICU (cardiac and non-cardiac)	Chart review Prospective data collection	226	NR/Unable to determine	NR/Unable to determine	NR
E - Others											
Baslaim 2006	NR	Retrospective cohort	Saudi Arabia	1	2000-2004	PCICU (cardiac only)	Chart review	26	Consecutive	Neonates Infants Children	Mean 16.4 mo [range 0.5-144]
ElBassetAboElEzz 2017	NR	Prospective cohort	Egypt	1	2014-2015	PICU of unknown composition	Prospective data collection	40	NR/Unable to determine	Children Adolescents	Age of patient group ranged from 1.5 to 8.5 yr with mean age of 4.9
Faraoni 2015	NGO	Retrospective cohort	Belgium	1	2010-2012	PCICU (cardiac only)	Registry	150	Consecutive	Infants Children	Median 14 mo [5-40]
Jhang 2018	NR	Retrospective cohort	South Korea	1	2013-2017	PICU (non-cardiac only)	Chart review	89	Consecutive	Neonates Infants Children Adolescents	Median 117.3 mo [range 0-286.4]
Leeper 2017	NR	Prospective cohort Observational/ descriptive study	USA	1	2015-2016	Emergency room (ER)	Prospective data collection	133	Consecutive	Infants Children Adolescents	Median 10 yr [IQR 5-13]
Leeper 2018	NGO	Prospective cohort Observational/ descriptive study	USA	1	2015-2017	PICU (non-cardiac only)	Prospective data collection	101	Consecutive	Infants Children Adolescents	Median 8 yr [IQR 4-12]
Lin 2017	NGO	Prospective cohort Observational/ descriptive study	Taiwan	1	2012-2015	PICU of unknown composition	Prospective data collection	42	Consecutive	Infants Children	Median 4.1 yr [IQR 1.7-8.7]
Liras 2015	NR	Retrospective cohort	USA	1	2010-2013	Emergency room (ER)	Registry	1819	Consecutive	Children Adolescents	Hyperfibrinolytic group median 11 yr [IQR 4-15], non hyperfibrinolytic group median 15 yr [IQR 9-16] p<0.001
Liras 2017	NR	Retrospective cohort	USA	1	2010-2016	Emergency room (ER),NR/Unable to determine	Registry	956	Consecutive	NR/Unable to determine	Coagulopathic group median 14 yr [IQR 6-16], control group median 15 yr [IQR 9-16], p=0.008
Moxon 2015	NR	Prospective cohort	Malawi	1	2008-2011	NR/Unable to determine	Chart review Prospective data collection	malaria patients =267; controls =135	NR/Unable to determine	NR/Unable to determine	Retinopathy (+) malaria: median 45 mo (95%CI 33-62); retinopathy (-) malaria: 45 mo (95%CI 28-52)
Oladunjoye 2018	NR	Prospective cohort	USA	1	2015-2016	PCICU (cardiac only)	Prospective data collection	202	Consecutive	Neonates Infants Children	Median age at surgery 0.4 yr [IQR 0.1-2.3]

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Rajkumar 2017	NR	Prospective cohort Observational/ descriptive study	India	1	2015-2016	NR/Unable to determine	Prospective data collection	87	NR/Unable to determine	Infants Children	Range 6 mo-14 yr
Rajpurkar 2019	Govt.	Non-randomized/quasi randomized controlled trial	NR	NR	Other (oncology units)	Prospective data collection	79	Consecutive	Children Adolescents	NR	NR
Schmidt 2018	Industry	Randomized controlled trial (RCT) cross-over RCT pragmatic RCT	USA	1	NR	NR/Unable to determine	Prospective data collection	162	Consecutive	Neonates Infants Children Adolescents	Median 7 mo [range 2 days - 17 yr]
Schneider 2011	NR	Prospective cohort	France	1	NR	PICU of unknown composition	Chart review Prospective data collection	49 (25 control; 24 patients)	NR/Unable to determine	Children Adolescents	Median 9.7 yr [range 2-17]
Schochl 2011	NR	Retrospective cohort	Austria	1	2005-2010	NR/Unable to determine	Chart review Prospective data collection	88	NR/Unable to determine	Adolescents	Mean 48yr [range 13-87]
Selim 2005	NR	Prospective cohort	Egypt	1	NR	Other (NICU)	Prospective data collection	33	NR/Unable to determine	Neonates	NR
Selladurai 1997	NR	Retrospective cohort Case series (patients compiled in serial fashion lacking a control group)	Malaysia	1	NR	NR/Unable to determine	Chart review Prospective data collection	204	NR/Unable to determine	NR/Unable to determine	NR
Thebaud 1999	NR	Case series (patients compiled in serial fashion lacking a control group)	France	1	1986-1994	PICU of unknown composition	Chart review Prospective data collection	14	Consecutive	Infants Children	Range 2-33 mo
Tzanetos 2012	Govt.	Prospective cohort Case series (patients compiled in serial fashion lacking a control group)	USA	1	NR	PCICU (cardiac only)	Prospective data collection	16	Consecutive	Neonates Infants Children	+ thrombus (n=5): mean 196.8 days (368.7); no thrombus (n=11): mean 518.7 days (436.2)
Vogel 2013	NR	Retrospective cohort Case series (patients	USA	1	2009-2011	Mixed PICU (cardiac and non-cardiac)	Chart review Prospective data collection Registry	86	Consecutive	Children Adolescents	Median 8yr (all</=14yr of age) [IQR 3, 12]

		compiled in serial fashion lacking a control group)									
Zavadil 1998	NR	Retrospective cohort	USA	1	1992-1997	NR/Unable to determine	Chart review Prospective data collection	30	Consecutive	Neonates	Hemorrhage group (n=13): mean 46.7 hours (75.5); non-hemorrhage cohort (n=17): mean 39.1 hours (70.0) (cohorts defined by amount of transfusions received)
Zinter 2016	NR	Prospective cohort	USA	5	2008-2014	Mixed PICU (cardiac and non-cardiac)	Prospective data collection	259	Consecutive	Infants Children Adolescents	Median 5.2 yr [IQR 1.1-13.2]
Zubair 2015	NR	Retrospective cohort Observational/ descriptive study	USA	1	2008-2014	Other (pre-op testing)	Chart review Prospective data collection	402	NR/Unable to determine	Infants Children	Median 2.3 yr [IQR 0.5-9.3]

Abbreviations: Govt., government; NGO, nongovernmental organization; NR, not reported; PICU, pediatric intensive care unit; PCICU, pediatric cardiac intensive care unit; IQR, interquartile range
Age presented as mean (SD) or median [range, IQR]
[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 Coagulation Dysfunction in Critically Ill Children (n=86 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
A - Platelets						
Agrawal 2008	Platelet count	Derivation	General PICU population (mixed cardiac and non-cardiac)	day 1, day 4 and day 7 of PICU admission	Mortality	AUROC: 0.84 for drop in platelet count aOR: 4.15 (1.05-16.3) aOR of death for platelet count <150K
Algren 1993	Coagulation times	Validation	Sepsis Other (confirmed meningococcal infection)	first hour of hospitalization (ED or ICU)	Mortality	
Anton-Martin 2017	Coagulation times Platelet count Other (anti-FXa)	Derivation	Other (ECMO)	24 and 72 hours before intracranial bleed or infarct for cases, equal date from cannulation for controls	Other (Cerebral Hemorrhage)	Other: No significant differences in median platelet count, PT, PTT, ACT, fibrinogen, and D-dimer between cases of intracranial hemorrhage and controls. Lower maximum anti-Xa level in the hemorrhage group but still within target
Choi 2017	Platelet count		Sepsis	PICU day 1 (1st hour)	Mortality	Se: 71.4 for all, 78.6 for heme-onc, 85.7 for non heme-onc Sp: 71.0 for all, 66.7 for heme-onc, 78.9 for non-heme onc PPV: 45.5 for all, 57.9 for heme-onc, 42.9 for non-heme-onc NPV: 88.0 for all, 84.2 for heme-onc, 96.8 for non-heme-onc AUROC: platelet count AUROC 0.796 p=0 CI 0.69-0.90 for all, 0.722 p=0.024 CI 0.55-0.89 for heme-onc, 0.857 p=0.003 CI 0.70-1 for non-heme-onc Youden's index: platelet cutoff 52K for all patients 30.5K for heme-onc, and 106K for non-heme-onc aOR: 0.988 CI 0.988 (0.977-0.999) for platelet count association with mortality
Chua 1993	Coagulation times Platelet count	Derivation	Other (clinical diagnosis of dengue shock syndrome or dengue hemorrhagic fever)	Hospital day 1	Mortality,Other (Bleeding)	Se: prolonged PT had sensitivity of 56.2% for bleeding, Sp: prolonged PT and specificity of 61% for bleeding PPV: prolonged PT had PPV 84% for bleeding, prolonged PTT had PPV 77% for bleeding NPV: Prolonged PTT had NPV 23% for bleeding Other: one way ANOVA, p <0.001 for Death with prolonged PTT >30 sec. One way Anova showed no association with mortality for prolonged PT.
Couto-Alves 2013	Coagulation times Platelet count Other (Fibrinogen level)	Derivation	Other (meningococcal sepsis)	first recorded sample	Mortality	LR: composite of base excess and platelet count LR test p<0.001, Hosmer-Lemeshow chi square test=20.2, p=0.009 Goodness of fit: composite of base excess and platelet count goodness of fit Nagelkerke pseudo-R2 =0.3 and Brier score =0.046. Calibration of the BEP score on the entire consortium dataset shows a relatively small underestimation of the probability of death for BEP > 0.3 (the mean absolute error is 0.025 and the 0.9 quantile of the absolute error is only 0.066

Ersoy 2007	Platelet count Coagulation factor concentration or activity Other (AT and fibrinogen)	Derivation	Sepsis	not clear- at time of diagnosis of sepsis	Mortality	Se: AT level of 15mg/dl=92.3%, fibrinogen level of 150mg/dL =92.3% Sp: AT level of 15mg/dl =61.9%, fibrinogen level of 150mg/dL =80.9% PPV: AT level of 15mg/dl =60.0%, fibrinogen level of 150mg/dL =25% NPV: AT level of 15mg/dl =92.8%, fibrinogen level of 150mg/dL =61.7% aOR: platelet count was not significant for mortality, AT level had OR 0.54, CI 0.37-0.96, p=0.002 for mortality,
Graciano 2005	Coagulation times Platelet count Other (fibrinogen)	Derivation	General PICU population (only non-cardiac)	worst value throughout PICU stay	Mortality	Other: Correlation between hematologic dysfunction, quantified using the worst fibrinogen level (mol/L), and the pediatric intensive care unit mortality rate. R =0.98, p =.0035
Housinger 1993	Platelet count	Other (descriptive)	Other (Burned patients)	varied- lowest platelet count and duration of platelet count < 0.1 x10 to the 12th/L	Mortality	Other: only Chi Squared, Survivors had mean days of 2.7 +- 10 of platelet count less than 0.1 x 10 th the 12th/L vs 8.3 +-9.0 days for nonsurvivors
Hu 2017	Coagulation times Platelet count	Other (derivation and validation cohorts reported)	Other (TBI; develop score to predict progressive hemorrhagic injury)	on admission to PICU	Other (progressive intracranial/cerebral parenchymal hemorrhage)	Other: C-statistic; 0.873 (95% CI 0.806-0.904)
Huang 2011	Coagulation times Platelet count Other (fibrinogen)		Sepsis Other (acalculous cholecystitis)	at time of diagnosis	Mortality	Other: descriptive statistics comparing survivors vs non-survivors; p-value determined
Isguder 2016	Platelet count Other (mean platelet volume)		General PICU population (mixed cardiac and non-cardiac)	admission and @72hrs; values for PLT count and MPV compared between the time points (delta value) and compared survivors to non-survivors	Mortality	aOR: parameters for MPV &MPV & deltaMPV higher in non-survivors MPV: p=0.003, dMPV p=0.001,OR 6.4)
Jhang 2016	Coagulation times Platelet count DIC		General PICU population (only non-cardiac) Other (labs available to calculate DIC score)	admission to study	Other (utility of DIC score to assess risks and compare to severity of illness scores)	AUROC: JAAM DIC score 0.788 (95% CI: 0.675-0.924); ISTH DIC score 0.716 (95% CI: 0.598-0.834) aOR: JAAM DIC score: OR 5.287; ISTH DIC score: OR 4.091 re: mortality prediction
Kalkwarf 2018	Coagulation times Platelet count Other (TEG)	Derivation	Trauma	on admission	Mortality	Se: Max Amp < 30mm Sensitivity 11%; Ly30>50% Sensitivity 14%;INR>3.0 Sensitivity 12%, Platelet count <30,000 Sensitivity 1% Sp: Max Amp < 30mm Specificity 100%; Ly30>50% Specificity 100%; INR>3.0 Specificity 100%; Platelet count <30,000 Specificity 100%% PPV: Max Amp < 30mm 100%; Ly30>50% 100%; INR>3.0 PPV 100%; Platelet count <30,000 PPV 100% NPV: Max Amp < 30mm NPV 93%; Ly30>50% NPV 93%; INR>3.0 NPV 92%; Platelet count <30,000 NPV 92% AUROC: Max Amp < 30mm AUROC 0.554; Ly30> 0.571 INR >3, AUROC 0.515; Platelet count <30,000 AUROC 0.505

Kamal 2011					Functional outcomes /residual morbidity	Se: Thrombocytopenia as a risk for poor outcome: sensitivity, 47.6%, (95% CI=25.7%-70.2%) Sp: Thrombocytopenia as a risk for poor outcome: specificity, 77.4% (95% CI=63.8%-87.7%) PPV: PFP (percentage fall of platelet count) of 50% as a risk for poor outcome: PPV was 81.8% (95% CI=59.7%-94.8%). Thrombocytopenia as a risk for poor outcome: PPV, 54.6% (95% CI=24.4%- 67.7%) NPV: PFP (percentage fall of platelet count) of 50% as a risk for poor outcome: NPV was 78.9% (95% CI=65.3%- 88.9%) . Thrombocytopenia as a risk for poor outcome: NPV, 78.9% (95% CI=65.3%-88.9%) LR: PFP (percentage fall of platelet count) of 50% as a risk for poor outcome: LR was 6.98. Thrombocytopenia as a risk for poor outcome: +LR, 2.1 AUROC: PFP (percentage fall of platelet count) AUROC 0.831 (95% CI=0.728 - 0.935) Youden's index: From the ROC analysis (Figure 5) and use of Youden's index (J), the optimum cutoff point of PFP (percentage fall of platelet count) was set at 51.5% aOR: PFP (percentage fall of platelet count) of 50%: OR was 16.8 (95% CI=4.7- 59.8)
Kilpi 1992	Platelet count	Derivation	Other (bacterial meningitis)	day 1,2,4 and 8 of hospitalization	Mortality	Other: No adjusted analysis, patients who died had lower platelet counts than those who survived, p<0.01
Kornelisse 1997	Coagulation times Platelet count DIC	Derivation	Sepsis,Other (meningococcal septic shock)	not specified but appears to be upon admission	Mortality	Other: Logistic regression analysis identified platelet count as being independently associated with likelihood of survival. Further analysis not reported.
Krishnan 2008	Platelet count	Derivation	General PICU population (mixed cardiac and non-cardiac)	at admission to PICU	Mortality	aOR: By logistic regression analysis, Thrombocytopenia at admission was predictive of increased mortality (OR 8.5, CI 2.9 -25; p <0.001). Thrombocytopenic at some point of pediatric intensive care unit stay with those who were never thrombocytopenic had OR 23.8 (95% CI 5.2-108.6), p < 0.0005; and f patients not thrombocytopenic at admission who developed thrombocytopenia during their pediatric intensive care unit stay with those who did not develop any thrombocytopenia had OR 18.6 (95% CI 3.2-107.3) p<0.0005
Lal 2011	Coagulation times Platelet count	Derivation	Other (acute on chronic liver failure)	not clearly specified, but after hospital admission	Mortality	Se: INR of 3.05 had a sensitivity of 100% for mortality Sp: INR of 3.05 had a specificity of 76%, PPV: INR of 3.05 had a positive predictive value of 44.45%, NPV: INR of 3.05 had a negative predictive value of 100% AUROC: INR: 0.917 (95% CI 0.815-1.019) Other: INR of 3.05 had a diagnostic accuracy of 80%

Malley 1996	Coagulation times Platelet count Other (fibrinogen)	Derivation	Sepsis Other (invasive meningococcal disease)	upon admission	Other (Adverse outcome was defined as death during hospitalization, limb amputation, or loss of all five digits on an extremity)	Se: In validation data: 2 of 3 factors (ANC < 3K, fibrinogen<250 mg/dl or platelet count <150K) was 82% Model using ANC<3K and fibrinogen <250mg/dl was 89% Sp: In validation data: 2 of 3 factors (ANC < 3K, fibrinogen<250 mg/dl or platelet count <150K) was 97% Model using ANC<3K and fibrinogen <250mg/dl was 97% PPV: In validation data: 2 of 3 factors (ANC < 3K, fibrinogen<250 mg/dl or platelet count <150K) was 82% Model using ANC<3K and fibrinogen <250mg/dl was 89% NPV: In validation data: 2 of 3 factors (ANC < 3K, fibrinogen<250 mg/dl or platelet count <150K) was 97% Model using ANC<3K and fibrinogen <250mg/dl was 97% aOR: PT >20s and PTT >60 sec were not significantly associated with adverse outcomes. Platelet count < 150K had aOR 6.2 (CI 1-36, p=0.04), and fibrinogen <250mg/dl had OR 42.7 (CI 4-460, p=0.002) for adverse outcome
Martins 2015	Platelet count	Validation	Sepsis Other (invasive meningococcal disease)	first hour of hospital admission	Mortality	Se: composite score of base excess and platelet count with cut off of 0.06 had sensitivity of 83% Sp: composite score of base excess and platelet count with cut off of 0.06 had specificity of 83% AUROC: composite score of base excess and platelet count had an AUROC 0.81 (0.66 - 0.97)
Mitra 2017	Coagulation times Platelet count		Sepsis		Mortality,Other (DIC)	Se: 70.8% Sp: 82.7% PPV: 72.3% NPV: 81.6% Other: Plasma fibrinogen level was found to be significantly higher among neonates with sepsis when compared to neonates in control group (p < 0.0001). It had sensitivity of 70.8 %, specificity of 82.7 %, positive predictive value (PPV) of 72.3 % and negative predictive value (NPV) of 81.6 % for diagnosis of neonatal sepsis at cut-off value of 301.90 mg/dL. When neonates with septic shock and/or disseminated intravascular coagulation (DIC) were excluded from study population, sensitivity and NPV rose to 91.9 % and 95.4 % at the same cut-off value while specificity and PPV remained the same. Lower level of plasma fibrinogen was detected in neonates with septic shock and/or DIC (p < 0.0001) and in neonates who died (p < 0.0001).
Mitsiakos 2015	Coagulation times Platelet count Other (mean platelet volume; platelet mass)	Sepsis Other (Gram negative sepsis)	day of dx of sepsis, day 2, day 3	Mortality		AUROC: The median PLT count and PM at days 1, 2, and 3 after diagnosis of gram-negative sepsis was significantly associated with the presence of ICH. Regression analysis revealed the cutoff predictive value of 355 fL/nL for the PM at day 3 (area under the curve: 75, sensitivity 90%, P=0.002). Other: The median PLT count and PM at days 1, 2, and 3 after diagnosis of gram-negative sepsis was significantly associated with the presence of ICH. Regression analysis revealed the cutoff predictive value of 355 fL/nL for the PM at day 3 (area under the curve: 75, sensitivity 90%, P=0.002).

Niederwanger 2018	Coagulation factor concentration or activity Other (AT)	Derivation	Sepsis	AT levels obtained at time of peak CRP +/- 3 days	Mortality,Organ-specific outcomes/residual morbidity	AUROC: for mortality in children < 1 yo with threshold of 41.5 AUROC 0.83 (0.67 to 0.99) in children > 1 yo with threshold of 67.5 AUROC 0.68 (0.55 to 0.80) aOR: for < 1 yo cut off AT 41.5: mortality 18.8 (1.74-1005.02) CV failure 1,97 (0,41-9.63) CNS failure2.57(0.03-213.54) Intestinal failure1.32(0.18-7.98)kidney1.29(0.1-10.78)liver0(0- .16) Respiratory6.23(1.23-37.81) MODS1.39(0.3-6.92) Bleeding 2.57(0.03-213.54)clotting 4.46(0.44-61.51): OR for > 1 yo cut off AT 67.5mortality 4.46(1,54-14.89) CV failure 1.53 (0.54-4.5) CNS failure 2.67 (0.57-16.82) Intestinal failure 4.04(0.97-24.08) kidney 1.09(0.43-2.77) liver 15.55(2.16-685.01) Respiratory 1.31(0.52-3.35) MODS 1.28(0.58-2.84) Bleeding 4.46(0.42-225.31) clotting 1.07(0.08-15.21)
Oren 2005	Coagulation times Platelet count DIC		Other (DIC)	at time of diagnosis w/subsequent interval not specified	Mortality	Other: descriptive statistics comparing survivors vs non-survivors for each parameter - calculating p-value; none of the measured lab parameters (Hb, WBC, PLT, PT, aPTT, FBGN, D-dimer, FDPs) predicted mortality
Patregnani 2012	Coagulation times Platelet count		Trauma	on admission	Mortality	Other: % mortality, descriptive statistics; coagulopathy defined as INR>/=1.5
Pone 2016	Platelet count Other (pulmonary or GI bleeding)		Sepsis	admission to study w/subsequent interval not specified		LR: positive likelihood ratio (significant >5.0); negative likelihood ratio (<0.20); hx of hemorrgage or thrombocytopenia did not meet either threshold
Purbiya 2018	Platelet count Other (PDW and PDW/PC ratio)	Validation	General PICU population (mixed cardiac and non-cardiac)	first lab after admission	Mortality	Se: Platelet count: 77.1 PDW: 51.4% PDW/PC: 80% Sp: Platelet count: 75.8% PDW: 73.1% PDW/PC: 75.2% AUROC: Platelet count: 0.80 PDW: 0.665 PDW/PC: 0.811
Reed 2010	Coagulation times Platelet count		Other (ECMO; autopsy data)	admission to study w/subsequent interval not clear - manuscript NOT in English	Other (thrombosis or hemorrhage on autopsy)	Other: % patients with finding; no correlation of hemorrhage or thrombosis with any parameters measured (PT, aPTT, FBGN, ACT, PLTs, hepain dose)
Rinka 2008	Platelet count		Other (Hemorrhagic Shock Encephalopathy Syndrome)	on admission	Mortality,Functional outcomes /residual morbidity	Other: descriptive statistics; PLT count not predictive of outcome
Silva 2007	Platelet count Other (CBC/ANC; Platelet x Neutrophil product as a predictor of outcome)	Derivation	Other (meningococcal disease)	on admission	Mortality	Se: PN product </= 113: 28.6% (95% CI: 86-58.1) Sp: PN product </= 113: 96.6% (95% CI: 888.1-99.5) PPV: PN product </= 113: 66.7% NPV: 84.8% PN product </= 113: AUROC: PN product </= 113: 0.85 (95% CI: 0.74-0.92)
Sreenivasan 2018	Platelet count Other (Platelet count was only useful in setting of hematocrit >40%)	Derivation	Other (serologically proven dengue fever)	daily during hospital admission	Other (severe dengue per WHO definition)	aOR: Hematocrit ≥0.40 concurrent with PC <100 × 109/L had an OR 2.985 (95%CI 1.783-4.997) and an adjusted OR 2.252 (95%CI 1.302-3.894) for severe dengue versus non severe dengue
Tekin 2019	Other (neutrophil to lymphocyte and platelet to lymphocyte ratios)	Derivation	Trauma	time of admission	Mortality	LR: NLR (OR, 3.21; P=0.048), PLR (OR, 0.90; P=0.032)
Trifa 2014	Platelet count		Sepsis	admission to study w/subsequent interval not clear - manuscript NOT in English	Functional outcomes /residual morbidity,Other (association of platelet count with	Other: thrombocytopenia (<100k) assoc with great incidence of gr (-) agents and with Klebsiella compared to infections in patients w/o thrombocytopenia

					agent causing infection)	
Whittaker 2013	Coagulation times Platelet count		Trauma	on admission	Mortality	aOR: 4.0 if coagulopathy present; modestly increased in non-TBI and more significantly increased in TBI patients; mortality higher in younger (<3y) patients in
Ye 2018	Platelet count Other (platelet volume parameters)	Derivation	General PICU population (mixed cardiac and non-cardiac),Other (mechanical ventilation)	trend over first 72 hours in PICU	Mortality	aOR: mortality in children, aged from 28 days to 3 years: PLT,109/l 0.99 (0.99, 1.00) NS MPV, fl 0.98 (0.96, 1.01) NS Plateletcrit, % 12.85 (0.00, 13711.72) NS; mortality in children, aged between >3 and 16 years PLT,109/l 1.01 (1.00, 1.01) P¼0.02 Plateletcrit, % 0.0 (0.00, 469.97) NS PDW, % 1.00 (0.98, 1.02) NS
ZafraAnta 1994	Coagulation times Platelet count		Other (acute liver failure)	admission to study w/subsequent interval not clear	Mortality,Functional outcomes /residual morbidity,Organ-specific outcomes/residual morbidity	Unable to determine
B - INR						
Algren 1993	Coagulation times	Validation	Sepsis Other (confirmed meningococcal infection)	first hour of hospitalization (ED or ICU)	Mortality	
Borgman 2011	Validation	Trauma	not clear- assume on admission	Mortality		AUROC: composite INR, base deficit and GCS had AUROC of 0.89 CI 0.87-0.92 associated with mortality aOR: INR 2.19 (1.5-3.3) associated with mortality
Cheuk 2004	Coagulation times Other (macroscopic hemorrhage)	Derivation	Other (HSCT)		Mortality	aOR: Macroscopic hemorrhage OR 0.018 for survival (CI 0.001,0.710) p value 0.032, R2 0.904 Other: univariate analysis: macroscopic hemorrhage has RR of mortality is 5.33 (CI 1.92,14.8) p <0.001, coagulopathy has RR mortality of 4.50 (CI 1.22, 16.6)
Grandjean-Blanchet 2018	Other (BIG score: base deficit INR GCS)	Validation	Trauma	ED prior to ICU admission	Mortality	Se: BIG score ≥16 demonstrated a sensitivity of 0.93 (95% confidence interval [CI]: 0.76-0.98) Sp: 0.83 (95% CI: 0.78-0.87) AUROC: BIG score (0.97; 95% IC: 0.95-0.99)
Hu 2017	Coagulation times Platelet count	Other (derivation and validation cohorts reported)	Other (TBI; develop score to predict progressive hemorrhagic injury)	on admission to PICU	Other (progressive intracranial/cerebral parenchymal hemorrhage)	Other: C-statistic; 0.873 (95% CI 0.806-0.904)
Lal 2011	Coagulation times Platelet count	Derivation	Other (acute on chronic liver failure)	not clearly specified, but after hospital admission	Mortality	Se: INR of 3.05 had a sensitivity of 100% for mortality Sp: INR of 3.05 had a specificity of 76%, PPV: INR of 3.05 had a positive predictive value of 44.45%, NPV: INR of 3.05 had a negative predictive value of 100% AUROC: INR: 0.917 (95% CI 0.815-1.019) Other: INR of 3.05 had a diagnostic accuracy of 80%

Leeper 2015	Coagulation times	Derivation	Trauma Other (Abusive head trauma)	upon hospital admission	Mortality	AUROC: Not specific for INR also includes acidosis, age, and Injury severity score. AUROC=0.8044 aOR: Coagulopathy (INR ≥ 1.3) OR=7.33 (95% CI 5.69-9.44) p-value<0.001 Goodness of fit: The Hosmer-Lemeshow goodness-of-fit test has a nonsignificant p value, indicating adequate fit of our model
Leeper 2016	Coagulation times	Derivation	Trauma	admission to ICU	Mortality	Se: INR >1.3, 79.8%, INR>1.5 57.3% Sp: INR>1.3 = 77.6%; INR > 1.5 = 92.4% PPV: INR >1.3, 30.8%, INR>1.5 48.6% NPV: INR >1.3, 96.9%, INR>1.5 94.6% Youden's index: Admission INR of 1.3 showed the strongest correlation with J = 0.722 (sensitivity, 80.8%; specificity, 77.6%). aOR: admission INR of 1.3 or greater was the strongest independent predictor of mortality, with an odds ratio of 3.77 (1.95-7.32, p<0.001), admission INR >1.5 had OR of 4.78, CI 2.47-9.26, p<0.001)
Leeper 2016	Coagulation times	Derivation	Trauma Other (Abusive head trauma)	upon admission	Mortality	AUROC: INR >1.3 had AUROC of 0.8 aOR: INR > 1.3 had aOR 3.65, CI 2.13-6.26, p=0.045; a second logistic regression model incorporating additional variables, INR >1.3 had aOR of 6.25, p=0.006 and then aOR 5.27, p=0.007 Goodness of fit: the Hosmer-Lemeshow goodness-of-fit test has a nonsignificant p value, indicating adequate fit of our model. All values for the variance inflation factors are less than 10, indicating absence of collinearity among the remaining variables
Liu 2006	Coagulation times	Derivation	Other (Acute Liver Failure)	varied: Peak values during admission	Mortality	AUROC: composite score including INR, bilirubin and ammonia had AUROC 0.905 for mortality, composite score with PT, bilirubin and ammonia had AUROC of 0.885
Lu 2008	Coagulation times	Validation	Other (Acute Liver Failure)	varies: peak level during admission	Mortality	AUROC: composite variable including PT, bilirubin and ammonia had AUROC 0.806. The C index was 80.6 (95% CI, 65.7-95.3). Composite variable with INR, bilirubin and ammonia had AUROC of 0.86. The C index was 86.3 (95% CI, 75.6-97.4).
Lu 2013	Coagulation times	Validation	Other (Acute Liver Failure)	study entry which was when criteria for ALF were met, and then peak level within 7 days after study entry	Mortality,Other (liver transplant)	AUROC: For LUI score (LIU = 3.507 × peak total bilirubin (mg/dL) + 45.51 × peak INR (seconds) + 0.254 × peak ammonia (μmol/L)), AUROC =0.81, (CI 0.78-0.85, p<0.0001). Same score using admission values AUROC=0.76 (CI 0.72-0.79, p<0.0001)
McDiarmid 2002	Coagulation times Other (multiple serum chemistries including total bilirubin albumin)	Other (chronic liver failure)		Mortality,Other (move to ICU)		Other: INR found to be predictive of both endpoints on multivariate analysis; included in the all scoring systems compared
Patregnani 2012	Coagulation times Platelet count		Trauma	on admission	Mortality	Other: % mortality, descriptive statistics; coagulopathy defined as INR>/=1.5
Podolsky-Gondim 2018	Coagulation times Platelet count	Derivation	Trauma,Other (TBI requiring neurosurgery)	at admission	Mortality,Functional outcomes /residual morbidity	aOR: Fibrinogen (mg/dL) for worse GOS score at one month 0.96 0.8-0.9 and at 6 months 0.97 0.8-0.9 Prothrombin Time for worse GOS score at one month 16.4 0.8-321 and at 6 months 24.4 1.1-506 aPTT* for worse GOS score at one month 2.18 0.5-8.8 and at 6 months 2.37 0.5-9.7 Thrombocyte (count) for worse GOS score at one month 0.99 0.9-1.0 and at 6 months 0.99 0.9-1.0 0.

Ranucci 2019	Coagulation times Other (ROTEM)	Derivation	PCICU population (only cardiac)	prior to cardiac surgery (baseline), after protamine, on arrival in PICU, after 24 hours in PICU	Other (severe bleeding > 30ml/kg/24 hours)	Se: INR cut-off value at an INR of 1.47 had a sensitivity of 50% fibrinogen levels 150 mg dL-1 had sensitivity of 52%, Sp: INR cut-off value at an INR of 1.47specificity of 91% for SB fibrinogen levels 150 mg dL-1 a specificity of 85%, PPV: INR cut-off value at an INR of 1.47PPV of 69%.fibrinogen levels 150 mg dL-1 PPV of 60% for SB. NPV: INR cut-off value at an INR of 1.47 had NPV of 81% ;fibrinogen levels 150 mg dL-1 an NPV of 81% AUROC: INR had an AUROC of 0.826 (95% confidence interval = 0.721-0.904); The fibrinogen levels had an AUROC of 0.770 (95% confidence interval = 0.660-0.858); the (best) cut-off value was 150 mg dL-1, . combined INR and fibrinogen had an AUROC of 0.867 Youden's index: fibrinogen levels 150 mg dL-1 (Youden's index = 0.37)
Srivastava 2012	Coagulation times		Other (acute hepatic faiure with or without encephalopathy)	admission to study w/subsequent interval not specified; highest value of PT used for analysis	Mortality,Functional outcomes /residual morbidity	Other: descriptive statistics comparing survivors to non-survivors; PT>/=40.5s assoc w/increased mortality (p<0.0001)
TudeMelo 2010	Coagulation times		Trauma	on admission	Mortality	aOR: "coagulopathy" (defined as 2x lab control) OR mortality=3.10 (95% CI: 1.05-9.18)
Yang 2019	Coagulation times	Derivation	Other (venoarterial ECMO)	24 hour after ECMO initiation	Mortality	Other: hazard ratio : Pt > 6 seconds prolonged in multivariate analysis for 30 day mortality : 3.013 (1.126, 8.061)
C - Fibrinogen						
Couto-Alves 2013	Coagulation times Platelet count Other (Fibrinogen level)	Derivation	Other (meningococcal sepsis)	first recorded sample	Mortality	LR: composite of base excess and platelet count LR test p<0.001, Hosmer-Lemeshow chi square test=20.2, p=0.009 Goodness of fit: composite of base excess and platelet count goodness of fit Nagelkerke pseudo-R2 =0.3 and Brier score =0.046. Calibration of the BEP score on the entire consortium dataset shows a relatively small underestimation of the probability of death for BEP > 0.3 (the mean absolute error is 0.025 and the 0.9 quantile of the absolute error is only 0.066
Ersoy 2007	Platelet count Coagulation factor concentration or activity Other (AT and fibrinogen)	Derivation	Sepsis	not clear- at time of diagnosis of sepsis	Mortality	Se: AT level of 15mg/dl=92.3%, fibrinogen level of 150mg/dL =92.3% Sp: AT level of 15mg/dl =61.9%, fibrinogen level of 150mg/dL =80.9% PPV: AT level of 15mg/dl =60.0%, fibrinogen level of 150mg/dL =25% NPV: AT level of 15mg/dl =92.8%, fibrinogen level of 150mg/dL =61.7% aOR: platelet count was not significant for mortality, AT level had OR 0.54, CI 0.37-0.96, p=0.002 for mortality
Faraoni 2014	Other (fibrinogen)	Derivation	PCICU population (only cardiac) Other (CPB)	10 minutes after protamine administration	Other (postoperative bleeding)	Se: Fibrinogen <1.5g/L -->68.9%, FIBTEM MCF <3mm-->78.6% Sp: Fibrinogen <1.5g/L -->83.8%, FIBTEM MCF <3mm-->70% AUROC: fibrinogen level AUROC 0,78, CI 0.70-0.85), for FIBTEM MCF AUROC 0.73, (CI 0.63-0.81) aOR: for fibrinogen level OR 0.97 (CI 0.95-0.99, p=0.006)
Graciano 2005	Coagulation times Platelet count Other (fibrinogen)	Derivation	General PICU population (only non-cardiac)	worst value throughout PICU stay	Mortality	Other: Correlation between hematologic dysfunction, quantified using the worst fibrinogen level (mol/L), and the pediatric intensive care unit mortality rate. R =0.98, p =.0035
Huang 2011	Coagulation times Platelet count Other (fibrinogen)		Sepsis Other (acalculous cholecystitis)	at time of diagnosis	Mortality	Other: descriptive statistics comparing survivors vs non-survivors; p-value determined

Jevtic 2010	Coagulation times Coagulation factor concentration or activity Other (AT FVIII vWF fibrinogen)	Other (post-HSCT w/VOD)	day 0, 1, 7, 14	Other (development of VOD)		Other: descriptive
Malley 1996	Coagulation times Platelet count Other (fibrinogen)	Derivation	Sepsis Other (invasive meningococcal disease)	upon admission	Other (Adverse outcome was defined as death during hospitalization, limb amputation, or loss of all five digits on an extremity)	Se: In validation data: 2 of 3 factors (ANC < 3K, fibrinogen<250 mg/dl or platelet count <150K) was 82% Model using ANC<3K and fibrinogen <250mg/dl was 89% Sp: In validation data: 2 of 3 factors (ANC < 3K, fibrinogen<250 mg/dl or platelet count <150K) was 97% Model using ANC<3K and fibrinogen <250mg/dl was 97% PPV: In validation data: 2 of 3 factors (ANC < 3K, fibrinogen<250 mg/dl or platelet count <150K) was 82% Model using ANC<3K and fibrinogen <250mg/dl was 89% NPV: In validation data: 2 of 3 factors (ANC < 3K, fibrinogen<250 mg/dl or platelet count <150K) was 97% Model using ANC<3K and fibrinogen <250mg/dl was 97% aOR: PT >20s and PTT >60 sec were not significantly associated with adverse outcomes. Platelet count < 150K had aOR 6.2 (CI 1-36, p=0.04), and fibrinogen <250mg/dl had OR 42.7 (CI 4-460, p=0.002) for adverse outcome
McManus 1993	Coagulation times		Sepsis Other (SIRS)	at presentation, 1st 24hrs of care, at discharge	Mortality,Outcomes related to MODS	Se: FBGN=81%; aPTT=95% Sp: FBGN=95%; aPTT=90% PPV: FBGN=93%; aPTT=86% NPV: FBGN=88%; aPTT=97% Other: Coagulopathy (defined as a partial thromboplastin time > 50 secs or serum fibrinogen concentration < 150 mg/dL [4.4 mmol/L]) at the referral site or on ICU admission was identified as an excellent predictor of poor outcome: sensitivity, specificity, positive and negative predictive values of a low serum fibrinogen value, being 81%, 95%, 93%, and 88%, and of prolonged partial thromboplastin time, being 95%, 90%, 86%, and 97%, respectively.
Mitra 2017	Coagulation times Platelet count		Sepsis		Mortality,Other (DIC)	Se: 70.8% Sp: 82.7% PPV: 72.3% NPV: 81.6% Other: Plasma fibrinogen level was found to be significantly higher among neonates with sepsis when compared to neonates in control group (p < 0.0001). It had sensitivity of 70.8 %, specificity of 82.7 %, positive predictive value (PPV) of 72.3 % and negative predictive value (NPV) of 81.6 % for diagnosis of neonatal sepsis at cut-off value of 301.90 mg/dL. When neonates with septic shock and/or disseminated intravascular coagulation (DIC) were excluded from study population, sensitivity and NPV rose to 91.9 % and 95.4 % at the same cut-off value while specificity and PPV remained the same. Lower level of plasma fibrinogen was detected in neonates with septic shock and/or DIC (p < 0.0001) and in neonates who died (p < 0.0001).

Niederwanger 2018	Coagulation times Platelet count		Sepsis	time of peak CRP	Mortality	AUROC: The ROC analysis for survival predicted by fibrinogen, platelets and aPTT resulted in an AUROC of 0.74 (0.63-0.85), 0.71 (0.63-0.79) and 0.81 (0.73- 0.90), respectively. aOR: increase of 100 mg/dl in fibrinogen increases the survival chance by 26%,OR 1.35 (1.04 to 1.82) per 50 G/l platelets by 48.4% 1.94 (1.3 to 3.29) , and aPTT prolongation of 10 s increases the mortality risk by 20.8% 0.83 (0.69 to 0.96) .Patients presenting with hypofibrinogenemia have a significantly higher mortality rate than do patients with normo- or hyperfibrinogenemia: OR 28.42 (5.42-284.81), p < 0.0001.
Podolsky-Gondim 2018	Coagulation times Platelet count	Derivation	Trauma,Other (TBI requiring neurosurgery)	at admission	Mortality,Functional outcomes /residual morbidity	aOR: Fibrinogen (mg/dL) for worse GOS score at one month 0.96 0.8-0.9 and at 6 months 0.97 0.8-0.9 Prothrombin Time for worse GOS score at one month 16.4 0.8-321 and at 6 months 24.4 1.1-506 aPTT* for worse GOS score at one month 2.18 0.5-8.8 and at 6 months 2.37 0.5-9.7 Thrombocyte (count) for worse GOS score at one month 0.99 0.9-1.0 and at 6 months 0.99 0.9-1.0 0.
Ranucci 2019	Coagulation times Other (ROTEM)	Derivation	PCICU population (only cardiac)	prior to cardiac surgery (baseline), after protamine, on arrival in PICU, after 24 hours in PICU	Other (severe bleeding > 30ml/kg/24 hours)	Se: INR cut-off value at an INR of 1.47 had a sensitivity of 50% fibrinogen levels 150 mg dL-1 had sensitivity of 52%, Sp: INR cut-off value at an INR of 1.47specificity of 91% for SB fibrinogen levels 150 mg dL-1 a specificity of 85%, PPV: INR cut-off value at an INR of 1.47PPV of 69%.fibrinogen levels 150 mg dL-1 PPV of 60% for SB. NPV: INR cut-off value at an INR of 1.47 had NPV of 81% ;fibrinogen levels 150 mg dL-1 an NPV of 81% AUROC: INR had an AUROC of 0.826 (95% confidence interval = 0.721-0.904); The fibrinogen levels had an AUROC of 0.770 (95% confidence interval = 0.660-0.858); the (best) cut-off value was 150 mg dL-1, . combined INR and fibrinogen had an AUROC of 0.867 Youden's index: fibrinogen levels 150 mg dL-1 (Youden's index = 0.37)
Tirosh-Wagner 2011	Coagulation times Other (Rotating Cone Platelet Analyzer (CPA) and ROTEM)	PCICU population (only cardiac)	t1=pre-op, T2=post-bypass admit to PICU, T3=24hr post-op/bypass	Other patient-centered outcomes,Other (aim is to identify patients at risk for bleeding/who ultimately bleed)		Other: incidence of bleeding assoc with low pre-op wt, longer bypass time nd lower core temp; elevated PT and low fibrinogen pre-op identifies patients at risk for bleeding but not mortality; decreased Max Clot Firmness (ROTEM) post-by-pass predictive of patients who bleed; CPA not predictive of bleeding
D – D-dimer						
Chen 2017	Other (D-dimers)	Validation	Sepsis	PICU day 1	Mortality	Se: composite of D-dimers, BNP, albumin, bilirubin, and ventilation within 24 hours 0.857 Sp: composite of D-dimers, BNP, albumin, bilirubin, and ventilation within 24 hours 0.677 AUROC: composite of D-dimers, BNP, albumin, bilirubin, and ventilation within 24 hours : training set AUROC 0.854 (CI 0.826-0.881) and validation AUROC 0.844 (CI 0.816-0.873) Goodness of fit: composite of D-dimers, BNP, albumin, bilirubin, and ventilation within 24 hours X2=6.766, p=0.562

Foaud 2014	Other (D-dimers)	Derivation	Trauma Other (TBI)	Day 1, 3 and 14 of admission	Mortality	Se: D-dimer Day 1 of 10.5 =89.5%, D-dimer of 3.6 on Day 3=84.2%, D-dimer of 1.1 on Day 14=73.7% Sp: D-dimer Day 1 of 100%, D-dimer of 3.6 on Day 3=92.6%, D-dimer of 1.1 on Day 14=81.5% PPV: D-dimer of 3.6 on Day 3=89.3%,D-dimer of 1.1 on Day 14=73.7% NPV: D-dimer Day 1 of 93.1%, D-dimer of 3.6 on Day 3=89.3%, D-dimer of 1.1 on Day 14=81.5% AUROC: D-dimer 0.936, 0.930 and 0.784 with 95% CI (0.836 - 1.00, 0.836 - 1.00 and 0.640 - 0.927) respectively.
Oren 2005	Coagulation times Platelet count DIC		Other (DIC)	at time of diagnosis w/subsequent interval not specified	Mortality	Other: descriptive statistics comparing survivors vs non-survivors for each parameter - calculating p-value; none of the measured lab parameters (Hb, WBC, PLT, PT, aPTT, FBGN, D-dimer, FDPs) predicted mortality
Qi 2014	Coagulation times Other (procalcitonin)		Other (SIRS)	admission to study w/subsequent interval not clear - manuscript NOT in English	Mortality	AUROC: AUROC (procalcitonin)=0.875; OR=1.684, p<0.01; AUROC (D-dimer)=0.872; OR=1.003, p<0.01
Wang 2012	Coagulation times Other (soluble P-selectin)		Other (severe pneumonia)	on admission	Mortality	Se: D-dimer 0.7mg/dL: 90.5%; P-selectin 94.0mcg/L: 82.4% Sp: D-dimer 0.7mg/L: 90.5%; P-selectin 94.0mcg/L: 88.7%; for both together: 90.2%
E - Other						
Baslaim 2006	DIC	Derivation	PCICU population (only cardiac) Other (ECMO)		Mortality	Other: only reported p value for univariate analysis, DIC occurred in all 8 children who died compared to 0 deaths in those without DIC, p =0.002
ElBassetAboElEzz 2017	Other (vWF antigen)	Derivation	General PICU population (only non-cardiac)	day 1 and day 3 of admission	Mortality	Se: Day 1 VWF Antigen level: 94.2; Day 3 VWF Antigen level: 93.4% Sp: Day 1 VWF Antigen level: 83.1%; Day 3 VWF Antigen level: 81.7% AUROC: Day 1 VWF Antigen level: 0.942; Day 3 VWF Antigen level: 0.934 aOR: vWF Ag levels at day 1: 6.56 (CI 0.45- 0.96), p value 0.05
Faraoni 2015	Other (ROTEM CT A10 A20 MCF)	Derivation	PCICU population (only cardiac) Other (CPB)	10 minutes after protamine administration at end of cpb	Other (postoperative bleeding)	Se: CT >111s --> 60%, EXTEM A10 <38mm--> 88%, FIBTEM A10<3mm-->85%, ROTEM probability score >0.2-->93% (CI 0.77-0.99) Sp: CT >111s --> 74%,XTEM A10 <38mm--> 52%, FIBTEM A10<3mm-->62%, ROTEM probability score >0.2-->33% (CI 0.19-0.51) PPV: ROTEM probability score >0.2-->53% (CI 0.38-0.67) NPV: ROTEM probability score >0.2-->86% (CI 0.57-0.98) AUROC: EXTEM CT AUROC 0.67, CI 0.59-0.75, p<0.0001; EXTEM A10 AUROC 0.74, CI 0.66-0.81, p<0.001, A20 (AUROC 0.76, CI 0.69-0.83; p<0.001, MCF (AUROC 0.76, CI 0.68-0.83, p<0.001, FIBTEM A10 (AUROC 0.72, CI 0.64-0.80, p<0.001); A20 (AUROC 0.73, CI 0.65-0.81, p<0.001); MCF (AUROC 0.74, CI 0.66-0.82, p<0.001)
Jhang 2018	DIC	Validation	Sepsis	within 12 hours of admission	Mortality	AUROC: 28 day mortality: the JAAM DIC score was 0.765 (95% CI: 0.648-0.882), modified JAAM DIC score was 0.741 (95% CI: 0.625-0.857), and the ISTH DIC score was 0.679 (95% CI: 0.534-0.823) aOR: Mortality: JAAM DIC score aOR 1.55 (CI 1.08-2.21) p value 0.017 Modified JAAM DIC score aOR 1.40 (CI 1.02-1.94) p value 0.040

Leeper 2017	Other (TEG LY30 classify as shutdown (SD) normal or hyperfibrinolytic (HF))	Derivation	Trauma	at initial trauma assessment in ED	Mortality,Functional outcomes /residual morbidity,Other (DVT- only unadjusted analysis: Shutdown was significantly associated with incidence of DVT compared with either HF (p = 0.048) or normal physiology (p = 0.002))	Youden's index: LY30 of 0.8 showed the strongest correlation for both mortality and for poor outcome (mortality plus disability)
Leeper 2018	Other (TEG used to define fibrinolysis shutdown (LY30 < 0.9%))	Derivation	Trauma Other (please specify)	within 24 hours admission	Mortality	aOR: There was a dose response with an OR of 1.18, meaning that for every mL/kg plasma, there was an associated 18% increased odds of sustained SD Other: Plasma transfusion was independently associated with sustained fibrinolysis SD after controlling for severe TBI. Patients with both severe TBI and sustained fibrinolysis SD had poor outcome (75% mortality and 100% functional disability in survivors).
Lin 2017	Other (thrombomodulin)		Sepsis	Days 1 and 3 PICU	Mortality,Other (DIC, development of MODS)	AUROC: day 1 serum thrombomodulin levels had good discriminative power in predicting the development of DIC (AUROC = 0.881, cut-off point 5.71 mU/ml), multiple organ dysfunction syndrome (MODS) (AUROC = 0.740, cut-off point 4.71 mU/ml), and mortality (AUROC = 0.863, cut-off point 5.95 mU/ml).
Liras 2015	Other (TEG LY-30 (clot lysis at 30 minutes))	Derivation	Trauma	ED trauma room	Mortality	aOR: LY-30 > or equal to 3% has aOR 6.2 (CI 2.465-16.269, p <0.001)
Liras 2017	Other (TEG coagulopathy: The r-TEG values used to define coagulopathy (coagulopathic) were the presence of any of the following: activated clotting time >128 seconds a-angle 65 degrees maximum amplitude 55 mm lysis 30 minutes after maximum amplitude>3%)	Derivation	Trauma	Trauma activation in ED	Mortality	OR: simple logistic (unadjusted) model, coagulopathy had an odds ratio of 3.4 for 30-day mortality (95% CI 0.94 to 15.68; p ¼ 0.094).
Moxon 2015	DIC Other (soluble thrombomodulin)		Other (cerebral malaria)	admission to study w/subsequent interval not specified	Mortality	aOR: AUROC retinoparetinopathy (+) cerebral malaria OR=3.068 (95%CI: 1.085-8.609; p=0.035) vs non-fatal cerebral malaria; soluble thrombomodulin independ assoc with fatal outcome (OR=1.084 for each mg/mL increase (95%CI: 1.017-1.156)
Oladunjoye 2018	Coagulation times Other (anti-FXa)	Derivation	PCICU population (only cardiac) Other (post cardiac surgery receiving	daily	Other (major and clinically relevant non-major bleeding events	aOR: there was no association as long as aPTT was below 150 seconds (OR, 0.92; 95% CI, 0.77-1.10; P = .35). When aPTT exceeded 150 seconds, the odds of major or clinically relevant nonmajor bleeding doubled with each 10-second increase (OR, 1.72;

			therapeutic anticoagulation with UFH)		during treatment with therapeutic UFH)	95% CI, 1.21-2.42; P = 0.003; Anti-Xa did not correlate with major or clinically relevant nonmajor bleeding (OR, 1.11 per 0.1 IU/mL increase; 95% CI, 0.89-1.29; P ¼ .34), and no significant thresholds were identified using piecewise regression modeling
Padungmaneesub 2019	DIC Other (DIC plus AT levels; DIC plus protein C levels ; DIC plus thrombomodulin levels)	Derivation	General PICU population (mixed cardiac and non-cardiac)	after 1 day in PICU (>24hours)	Mortality,Other (bleeding and clotting events)	AUROC: bleeding and ISTH DIC score (AUROC = 0.732), ISTH DIC score plus PC (AUROC = 0.72), ISTH score plus AT (AUROC = 0.751) and ISTH DIC score plus AT and PC (AUROC = 0.738)
Rajkumar 2017	Coagulation times Other (Sonoclot POC testing)		Other (post-cardiac surgery)	pre-CBP, post-CBP, hr 4	Other (postoperative bleeding)	AUROC: AUROC for Sonoclot glass bead plt fxn strongest predictor of post-op bleeding: AUROC=0.725 (95%CI: 0.619-0.831)
Rajpurkar 2019	DIC	Derivation	Other (patients enrolled in COG AAML0631 clinical trial open to patients age 2 to below 22 years with previously untreated APL confirmed by PML-RARA reverse transcription polymerase chain reaction)	during induction therapy	Mortality,Other (bleeding or clotting outcomes)	Se: ISTH DIC score ≥ 6 in predicting patients experiencing at least 1 lethal or nonlethal coagulopathy event during induction was 70.6% (95% CI, 44.0%−89.7%) Sp: 64.5% (95% CI, 51.3%−76.3%)
Schmidt 2018	Other (oxygen reduction potential (ORP))	Derivation	Other (CPB)	pre CPB, post CPB, 6 hrs post CPB, 12 hours post CPB	Other (infection and thrombosis)	Other: descriptive p values showing reduced ORP at 6 and 12 hours post CPB was associated with increased rates of infection and thrombosis 0.002 and 0.0007 respectively.
Schneider 2011	Other (soluble thrombomodulin activity and ag procoagulant plasma phospholipids)	Other (post-BMT (8 auto, 16 allo))	1 week pre-BMT then	Mortality,Other (BMT complications)		Other: descriptive statistics regarding relative incidence of outcome; TM activity/TM ag ration decreased in patients with "poor outcome" (p<0.05); PPL decreased in "poor outcome"
Schochl 2011	Coagulation times Other (ROTEM)		Trauma	on admission	Mortality,Other (compared coagulation test with ROTEM as predictor for mortality: best predictors were: aPTT and ROTEM FIBEM MCF)	AUROC: mortality: aPTT: 0.79(95% CI: 0.686-0.868; p<0.001); MCF: 0.77(95% CI: 0.665-0.850; p<0.001)
Selim 2005	Other (soluble Fibrin Monomer complex)		Sepsis	dx/suspicion of sepsis	Mortality,Other (development of DIC)	Se: sFM cutoff of 48.5mg/L: 100% predictor of DIC Sp: sFM cutoff of 48.5mg/L: 93% predictor of DIC
Selladurai 1997	Coagulation times Other (DIC score determined from: PT aPTT FBGN PLT count FDPs TCT)	Derivation	Trauma	admission; subsequent testing not identified	Mortality	Other: derived DIC score along with aPTT & FDPs (components of DIC score) associated with CGS

Thebaud 1999	DIC		Other (Hemorrhagic Shock Encephalopathy Syndrome)	admission to study w/subsequent interval not identified	Mortality,Functional outcomes /residual morbidity,Organ-specific outcomes/residual morbidity	Other: descriptive statistics (i.e., % of patients with mortality or poor outcome)
Tzanetos 2012	Coagulation times Coagulation factor concentration or activity Other (urinary thromboxane thrombin-AT complex soluble CD40 Ligand)	Other (cardiac surgery for single ventricle physiology)	day 0, POD 1,3,5	Other (thrombus formation)		Other: % developing thrombus: lower AT (p=0.01), higher tPA ag (p=0.02) day#0; increased difference vs "no thrombus" cohort over time - AT p=0.002, tPA ag p=0.005
Vogel 2013	Coagulation times Other (TEG)		Trauma	on admission	Other (transfusion of blood products)	aOR: on multivariate analysis ACT, R-value, k-time, alpha-angle, MA all predicted RBC or plasma transfusion w/in 6hrs; MA predicted initiation of life sustaining intervention (OR=0.82; 95% CI: 0.70-0.96; p=0.018); all TEG parameters except LYS30 predicted mortality
Zavadil 1998	Coagulation times Other (TEG)		Other (ECMO)	pre-ECMO	Other (bleeding; noted more often in patients assigned to HEM group (per ELSO criteria))	Other: descriptive statistics comparing HEM vs non-HEM cohorts for risk of bleeding; p-value determined
Zinter 2016	Coagulation factor concentration or activity Other (angiopoietin-2)	General PICU population (mixed cardiac and non-cardiac)	days 1&3	Mortality		aOR: day1 angiopoietin OR for mortality=3.6 (1.1-12.1) and for increasing angio-2 from day1-d3: OR 3.3 (1.2-9.2)
Zubair 2015	Other (PFA-100)		PCICU population (only cardiac) Other (pre-operative cardiac surgery)	testing w/in 30d of surgery	Mortality,Other (platelet function by PFA-100)	Kaplan-Meier

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; AT, antithrombin; anti-FXa, anti-factor Xa; POD, postoperative day

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Research Priorities

We propose 4 scientific priorities.

1) To validate other biomarkers that can define coagulation dysfunction (e.g., von Willebrand factor, antithrombin, thrombomodulin, mean platelet volume, platelet distribution width, oxidation reduction potential, angiopoietin, platelet dysfunction and viscoelastic measures of hemostasis, such as thromboelastography or thromboelastometry). Each of these biomarkers should be tested in multicenter studies to enhance the external validity of the findings. Thresholds that maximize the sensitivity and specificity of each biomarker should be determined by analysis of study data rather than being set *a priori* and then analyzed against a determined outcome. Testing should also be standardized. Widespread use of thromboelastography and thromboelastometry has been hindered by lack of standardization of these assays. Lastly, the performance of these biomarkers singly and in combination with the proposed criteria for coagulation dysfunction should be evaluated.

2) To define coagulation dysfunction in children on mechanical circuits, such as extracorporeal membrane oxygenation, ventricular assist device and continuous renal replacement therapy. Given the severity of illness among children receiving these therapies, coagulation dysfunction is likely common and encompasses both excessive bleeding and pathologic thrombosis. However, the use of anticoagulation confounds the diagnosis of coagulation dysfunction under these conditions. Exclusion of aPTT values, a commonly used measure of anticoagulation in children on mechanical circuits, in our proposed criteria potentially limits confounding. In addition to anticoagulation while on mechanical circuits, the interaction between the blood and the mechanical circuit *per se* may have effects on the levels of the biomarkers included in our proposed criteria. Extracorporeal membrane oxygenation, for example, is known to affect platelet count and fibrinogen levels. Future studies should identify biomarkers of coagulation dysfunction that are specific to children on mechanical circuits, or perhaps, identify different thresholds using the same biomarkers in our proposed criteria. Included foci of investigation should be the development of abnormal platelet function (both hyper- and hypofunction) under these conditions and the clinical impact produced. It is also important to characterize the temporal course of the different

biomarkers after cessation of the mechanical circuit and/or anticoagulation. This will determine the time period when our proposed criteria are already valid in identifying coagulation dysfunction among children who were recently on mechanical circuits.

3) The third scientific priority is to test coagulation parameters, such as platelet count, INR, fibrinogen, D-dimer and others, as continuous variables with clinical measures of altered hemostasis, including excessive bleeding or pathologic thrombosis, as the outcome measure. Limited data informed our proposed criteria for coagulation dysfunction in critically ill children. A major limitation of the selected studies is that none identified threshold values for important parameters, i.e., platelet count, INR, fibrinogen, D-dimer and others, that resulted in abnormal hemostasis, such as excessive bleeding. Rather, they chose values based on prior studies and tested them for effect on a chosen outcome, most commonly mortality. While these values have been shown to be associated with an increased risk of mortality in the studied patient populations, there is minimal definitive data linking them with coagulation dysfunction, e.g., hemorrhage or pathologic thrombosis. There is also minimal data to indicate that the values chosen are indeed the appropriate and informative thresholds. In addition, the specificity of our proposed criteria is anticipated to be significantly better when multiple criteria are combined. However, studies investigating these combinations are not available. Consequently, these parameters should be tested singly and in combination.

4) The fourth research priority is to identify biomarkers of altered coagulation resulting in abnormal thrombus formation. Candidate biomarkers may be similar to those assessed as markers of hemorrhage risk and should be investigated in a parallel fashion in clinical studies in which the outcome measures include excessive bleeding or pathologic thrombosis. Given the role that endothelial cells play in the regulation of hemostasis, these studies will also need to consider including biomarkers of endothelial cell function or injury. Again, it is not sufficient to only identify an association with an outcome, but the preferred studies should identify a clinically meaningful threshold value for the biomarker.