S1-file: MEDLINE database search, flow diagram illustrating the literature selection process, and evidence assessment for the first query.

Query # 1: *"Does coagulopathy affect mortality in trauma?".*

PubMed search details: search date December 9 2014

((("blood coagulation disorders"[MeSH Terms] OR ("blood"[All Fields] AND "coagulation"[All Fields] AND "disorders"[All Fields]) OR "blood coagulation disorders"[All Fields] OR "coagulopathy"[All Fields]) AND ("injuries"[Subheading] OR "injuries"[All Fields] OR "trauma"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields])) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) AND ("2000/01/01"[PDAT]: "3000"[PDAT])

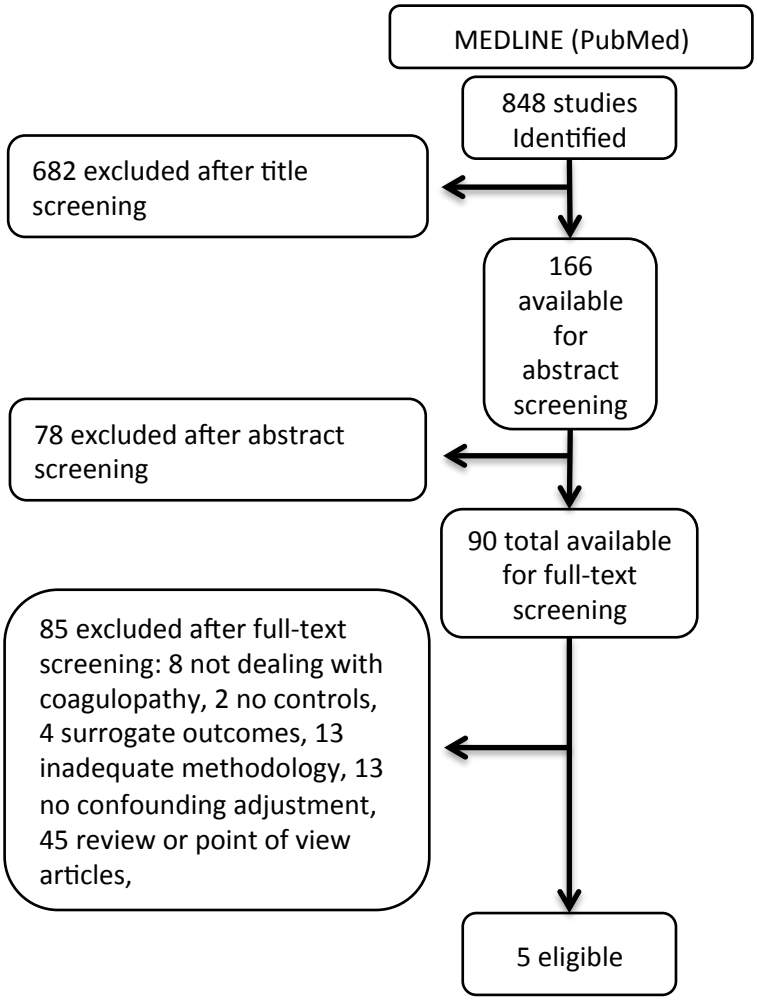
MEDLINE (PubMed)
848 studies Identified
682 excluded after title screening
166 available for abstract screening
78 excluded after abstract screening
90 total available for full-text screening
85 excluded after full-text screening: 8 not dealing with coagulopathy, 2 no controls, 4 surrogate outcomes, 13 inadequate methodology, 13 no confounding adjustment, 45 review or point of view articles,
5 eligible

Table S1

Observational study	1	Very low evidence - Downgraded study
Year	2014	
Journal	CC	
First Author	Hagemo	
Statistical method	Generalised additive regression and piecewise linear model	
Inclusion criteria	Patients initiating full trauma team response with time from injury to arrival within 180 minutes	
Risk factor	Fibrinogen and platelet reduction, INR increase	
Centres	4	**Outcome** 28-day mortality: NA **Variable: OR (95%-CI)**
N° patients/centre/year	NA	Low fibrinogen: 0.08 (0.03-0.20)
Study duration (days)	729	High fibrinogen: 1.77 (0.94-3.32)
Total (included in the model)	1133	INR: 1.65 (0.65-4.18) Platelet count: 1 (1.0-1.0)
	GRADE CRITERIA	
	Statistical reporting	Partial
	Methodological and statistical	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	Very large
	Residual confounding	Does not indicate upgrading
	Dose /response	Yes
	DETAILS	
Downgrading		
Up-grading	Dose /response: FFP:PRBC ratio significant as a continuous variable generated, however, by a probably biased model. Upgrading not indicated.	
External validity	Only two centres participating to the study, with, however, a high number of patients treated per centre	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Methodological and statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S1 (continued from the previous page)

Observational study	2	Very low evidence - Downgraded study
Year	2012	
Journal	JTH	
First Author	Rourke	
Statistical method	Logistic regression	
Inclusion criteria	Time fron injury to arrival within 120 minutes, SBP < 90 at admission, poor responsiveness to initial fluid administration	
Risk factor	Fibrinogen reduction, APTT increase	
		Outcome
		28-day mortality: 62 (12%)
Centres	2	**Variable: OR (95%-CI)**
N° patients/centre/year	86	Fibrinogen: 0.22 (0.10-0.47)
Study duration (days)	1095	APTT: 1.05 (1.01-1.09)
Total (included in the model)	517	
28-day mortality	62 (12%)	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose /response	Not applicable
	DETAILS	
Downgrading	Adequate control for confounding: Only four variables entered the final model, too few for explanatory purposes. Statistical reporting : Logistic regression. No Statistical support reported. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Variable selection method: Stepwise forward selection. Reporting of variable coding method not performed. Methodological and statistical quality: Insufficient statistical reporting. Important covariates are missing in the model (possible underfitting).	
Up-grading	Size of effect: The large fibrinogen OR reduction may be the result of a biased model. Upgrading is not indicated.	
External validity	Only four centres participating to the study, with, however, a high number of patients treated per centre	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Methodological and statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S1 (continued from the previous page)

Observational	3	Very low evidence - Downgraded study
Year	2010	
Journal	Injury	
First Author	Mitra	
Statistical method	Logistic regression	
Inclusion criteria	Patients receiving more than 4 packed red blood cell units within 4 hours from admission	
Risk factor	INR increase, Platelet count reduction	
Centres	1	**Outcome** 30-day mortality: 99 (29.9%) **Variable: OR (95%-CI)**
N° patients/centre/year	90	Platelet count: 0.99 (0.99-0.99)
Study duration (days)	1338	INR: 1.43 (1.02-2.01)
Total (included in the model)	331	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	Very large
	Residual confounding	Does not indicate upgrading
	Dose /response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Only 3 variables remained in the model an insufficient number for explanatory purposes. Statistical reporting: Logistic regression. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Variable selection method: Stepwise backward elimination. Reporting of variable coding method not indicated. Statistical quality: Possibly underfitted of the model.	
Up-grading	Size of effect: The 43% mortality risk with each unitary INR increase was generated by a potentially biased model. Upgrading not indicated.	
External validity	Single centre study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S1 (continued from the previous page)

Observational study	4	Very low evidence - Downgraded study
Year	2003	
Journal	JT	
First Author	MacLeod	
Statistical method	Logistic regression	
Inclusion criteria	All patients with trauma	
Risk factor	PT and APTT increase	
		Outcome
		Hospital mortality: NA
Centres	1	**Variable: OR (95%-CI)**
N° patients/centre/year	1272	PT: 1.35 (1.11-1.68)
Study duration (days)	2191	APTT: 4.26 (3.23-5.62)
Total (included in the model)	7638	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	GRADE overall	Yes
	Indirectness	Yes
	Imprecision	Yes
	Other	No
	Publication bias	very serious
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose /response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Insufficient number of variables for an explanatory model, variables were arbitrarily dichotomized. Statistical reporting: Logistic regression. No Statistical support reported. Checking for conformity with linear gradient for continuos variables not reported. Dichotomization of continuos variables. Test for interaction not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Variable selection method: Not Reported. Reporting of variable coding method not performed. Comments: Crude mortality rate of patients included in logistic regression not available. There were 1276 deaths out of 14397 patients in the overall cohort (8.9%). Statistical quality: Dichotomization of almost all continuos variables included in the model was not justified and thus was probably based on arbitrary cut-offs. The model did not include important predictors.	
Up-grading	Size of effect: Large effect for PTT, generated however by a potentially biased model. Dose /response: FFP:PRBC ratio significant as a continuous variable generated, however, by a probably biased model. Upgrading not indicated.	
External validity	Single centre study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	No
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S1 (continued from the previous page)

Observational study	5	Very low evidence - Downgraded study
Year	2011	
Journal	JT	
First Author	Sambasivan	
Statistical method	Logistic regression	
Inclusion criteria	Patients receiving at least one but less than 10 PRBC units within 24 hours from admission	
Risk factor	APTT increase	
Centres	23	**Outcome** Hospital mortality: 173 (14.6%) **Variable: OR (95%-CI)**
N° patients/centre/year	22	APTT: 1.015 (1.010-1.019)
Study duration (days)	851	
Total (included in the model)	1181	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	GRADE overall	Yes
	Indirectness	Yes
	Imprecision	Yes
	Other	No
	Publication bias	very serious
Up-grading	Size of effect	Very large
	Residual confounding	Does not indicate upgrading
	Dose /response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Only 4 variables remained in the model an insufficient number for explanatory purposes. Statistical reporting: Proportional hazards including propensity score. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Variable selection method: Stepwise forward selection. Reporting of variable coding method not indicated. Statistical quality: Hazard proporionals assumption not checked. Possible underfitting of the model.	
Up-grading	Size of effect: Very large protective effect generated, however, by a potentially biased model. No upgrading indicated. Dose /response: FFP:PRBC ratio significant as a continuous variable generated, however, by a probably biased model. Upgrading not indicated.	
External validity	Multicentre study, with sufficient number of patients per centre	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence