



Risk factors for trauma-induced coagulopathy- and transfusion-associated multiple organ failure in severely injured trauma patients

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Background: Both trauma-induced coagulopathy (TIC) and transfusion strategies influence early outcome in hemorrhagic trauma patients. Their impact on late outcome is less well characterized. This study systematically reviews risk factors for TIC- and transfusion-associated multiple organ failure (MOF) in severely injured trauma patients.

Materials and methods: A systematic search was conducted in PubMed and Embase. Studies published from 1986 to 2013 on adult trauma patients with an injury severity score ≥ 16 , investigating TIC or transfusion strategies with MOF as primary or secondary outcome, were eligible for inclusion. Results of the included studies were evaluated with meta-analyses of pooled data.

Results: In total, 50 studies were included with a total sample size of 63,586 patients. Due to heterogeneity of the study populations and outcome measures, results from 7 studies allowed for pooling of data. Risk factors for TIC-associated MOF were hypocoagulopathy, hemorrhagic shock, activated protein C, increased histone levels, and increased levels of markers of fibrinolysis on admission. After at least 24 h after admission, the occurrence of thromboembolic events was associated with MOF. Risk factors for transfusion-associated MOF were the administration of fluids and red blood cell units within 24 h post-injury, the age of red blood cells (> 14 days) and a ratio of FFP:RBC $\geq 1:1$ (OR 1.11, 95% CI 1.04–1.19).

Conclusion: Risk factors for TIC-associated MOF in severely injured trauma patients are early hypocoagulopathy and hemorrhagic shock, while a hypercoagulable state with the occurrence of thromboembolic events later in the course of trauma predisposes to MOF. Risk factors for transfusion-associated MOF include administration of crystalloids and red blood cells and a prolonged storage time of red blood cells. Future prospective studies investigating TIC- and transfusion-associated risk factors on late outcome are required.

Keywords: trauma, multiple organ failure, transfusion, coagulopathy, resuscitation

INTRODUCTION

Despite advances in trauma care, multiple organ failure (MOF) still remains one of the leading causes of late mortality (occurring after more than 3 days) in trauma patients (1, 2). The incidence of MOF in severely injured trauma patients ranges from 15% up until 40% (3–6), with an associated mortality rate that varies between 24% (3) and 51% (6). Even though MOF-related mortality has been shown to decrease over the last decades (2, 6), mortality is still 10 times higher in patients with MOF compared to patients without MOF (4, 5).

Over the last decade, trauma-induced coagulopathy (TIC) is increasingly recognized to contribute to adverse early outcome

in trauma patients (7–13). In recognition of that, transfusion strategies have changed toward more and earlier administration of plasma. This has led to a shift in the ratio of RBC:FFP to 1:1. Furthermore, fluid resuscitation with crystalloids has evolved from aggressive therapy to a minimal amount of crystalloid administration. More and earlier administration of plasma, combined with a restriction of crystalloid administration, has showed to reduce early mortality (14–16). However, the impact of both TIC and changing transfusion strategies on the occurrence of MOF has not been systematically reviewed before. Therefore, the aim of this study was to summarize risk factors for TIC- and transfusion-associated MOF in severely injured trauma patients.

MATERIALS AND METHODS

The present study was reported according to the PRISMA guidelines (preferred reporting items for systematic reviews and meta-analyses) (17).

Abbreviations: ED, emergency department; FFP, fresh frozen plasma; ISS, injury severity score; MOF, multiple organ failure; RBC, red blood cell; RCT, randomized controlled trial; rVII, recombinant factor VII; TIC, trauma-induced coagulopathy.

STUDY SELECTION

An electronic search was conducted in PubMed and Embase for articles published from 1986 to 2013. In addition, we searched for ongoing trials on www.controlled-trials.com and www.clinicaltrials.gov.

The following subject headings and free text words were used: (“Blood Coagulation Disorders”[Mesh] OR “Blood Coagulation”[Mesh] OR Coagulation[tiab] OR coagulopathy[tiab] OR “Fibrinolysis”[Mesh] OR Fibrinolysis[tiab] OR hypofibrinolysis[tiab] OR hyperfibrinolysis[tiab]) OR (“Blood Transfusion”[Mesh] OR Transfusion[tiab] OR “Transfusion Medicine”[Mesh] OR “Erythrocyte Transfusion”[Mesh] OR “Blood Component Transfusion”[Mesh]) AND (“Multiple Organ Failure”[Mesh] OR multiple organ failure*[tiab] OR MOF[tiab] OR (infection*[tiab] AND trauma[tiab])) AND (“Multiple Trauma”[Mesh] OR multiple trauma[tiab] OR “Wounds and Injuries”[Mesh] OR “Injury Severity Score”[Mesh] OR Injury Severity Score[tiab] OR ISS[tiab] (Table S2 in Supplementary Material).

Target population were trauma patients who suffered blunt or penetrating trauma, with a mean injury severity score (ISS) of ≥ 16 and an age of ≥ 16 years. Randomized controlled trials (RCTs) and observational studies investigating TIC or transfusion strategies with MOF as primary or secondary outcome were eligible for inclusion. Studies, which focused on patients with isolated traumatic brain injury or burn injury, were excluded. Both prospective and retrospective studies were included. Reviews, correspondences, case reports, expert opinions, and editorials were excluded. The search was conducted by two independent researchers (Kirsten Balvers and Mathijs R. Wirtz). Any discrepancies in the included studies were resolved by discussion between the reviewers. If necessary, an independent third reviewer was consulted. Only articles defining MOF according to the definition of the Denver (18), Marshall (18, 19), or SOFA (20) score were included in this review. A Denver score of more than 3 and a Marshall score of more than 5, both for at least two consecutive days, were used to define MOF. Furthermore, MOF according to the SOFA score was defined as the simultaneous failure of two or more organ systems. Organ failure was defined as a total of more than two points in a single organ. Language was limited to English, Dutch, or German. We reviewed the bibliographies of the eligible studies for citations of additional suitable studies.

DATA SYNTHESIS

Primary outcomes were risk factors for TIC- and transfusion-associated MOF. Since most of the studies in this field are observational studies, we performed a quality assessment according to the Newcastle-Ottawa Scale (21). Characteristics of the studies examined included comparability of the study groups, methods used to select study participants and determination of outcome variables. The quality of selection of patients in the included studies was rated as good if they included severely injured trauma patients and the control group was drawn from the same community as the exposed cohort. The assessment of comparability of the studies was based on the design and/or analysis used in the studies. Quality of outcome variables was determined by follow-up period and $< 10\%$ of patients lost-to-follow-up. The Cochrane Collaboration’s

tool for assessing the risk of bias was used to assess the quality of RCTs (22). This tool was used to evaluate RCTs on seven specific domains (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias). If the results of studies were contradicting, the quality assessment was used to grade conclusions.

Review Manager (RevMan 5, The Nordic Cochrane Centre) was used to combine findings of studies in a meta-analysis. Studies were pooled if homogeneity was considered by assessing study population, intervention, and outcome. RevMan was used to determine homogeneity by the inverse variance method for a random or fixed effects model. If homogeneity was not obtained studies were excluded from meta-analysis. Heterogeneity was expressed by I^2 . An I^2 of $> 75\%$ was considered as substantial heterogeneity. Meta-analysis was performed on observational studies and RCTs, in which data from observational studies and RCTs were not combined in the same meta-analysis. For the outcome of interest, risk ratios and 95% confidence intervals were used.

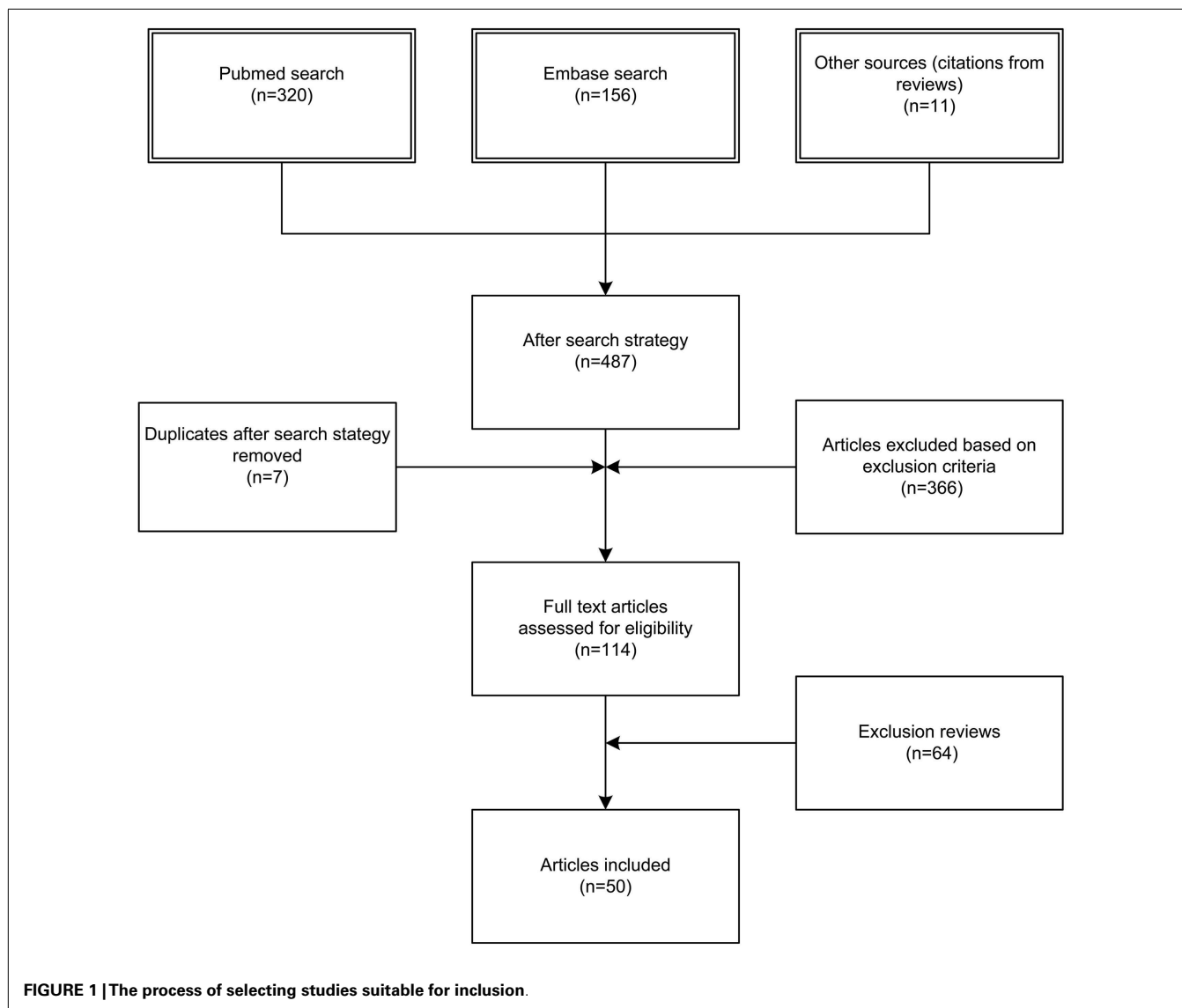
RESULTS

We identified 476 articles (PubMed 320, Embase 156) meeting the inclusion criteria. Of these, seven duplicates were removed. Reviewing of the bibliographies resulted in 11 additional articles. The full texts of 114 articles were assessed for eligibility. An additional 64 reviews were excluded, bringing the total on 50 included articles with a total sample size of 63,586 patients (Figure 1). Of the 50 included studies, 46 studies were observational cohort studies and 4 were RCTs. The observational studies included 15 retrospective and 31 prospective studies. Sample size in these studies varied between 19 and 20,288 patients with a median of 384 (IQR 135–1217) patients. Two studies included a heterogeneous population of intensive care patients, all other studies were restricted to trauma patients. The score of the included studies on the Newcastle-Ottawa scale ranged from 6 to 8 with a median of 7. The score of the Cochrane Collaboration’s tool for assessing the risk of bias ranged from 8 to 9 (Tables 1 and 2; Table S1 in Supplementary Material).

RISK FACTORS FOR TIC-ASSOCIATED MOF

Eighteen studies reported the effect of TIC on the development of MOF in trauma patients (Table 1). The presence of hypocoagulopathy on admission to the emergency department (ED) was an independent risk factor for MOF (26, 30, 33, 35–39); however, studies could not be pooled due to substantial heterogeneity ($I^2 = 90\%$, Figure 2). Hypocoagulopathy was defined by prolongation of coagulation parameters including PTT, INR, and APTT and a decreased platelet count (26). Four studies reported a decreased platelet count as an independent risk factor (23, 26, 41, 72). Of note, hypocoagulopathy was rare in patients without persisting shock (73). Other risk factors for TIC-associated MOF were activation of protein C, increased levels of fibrinolytic markers (27, 36–39), and increased levels of extracellular histones (37). Of note, these risk factors were reported in small study numbers.

Taken together, after trauma, damaged endothelial cells and extracellular histones activate protein C, which inhibits factor Va



and VIIa and leads to hyperfibrinolysis due to the consumption of plasminogen activator inhibitor, with subsequent hypocoagulopathy (37, 74–76).

Later in the course of events following trauma, patients tend to develop a hypercoagulopathy as reported in 5 studies with a total of 5581 patients. In these studies, an association between thromboembolic events, including disseminated intravascular coagulation (DIC) and venous thromboembolism (VTE), and MOF was reported (27, 28, 30, 32, 34). Pooling of data in a meta-analysis was not possible due to differences in outcome measures.

RISK FACTORS FOR TRANSFUSION-ASSOCIATED MOF

We found 36 studies reporting an association between transfusion and the development of MOF in trauma patients (Table 2).

Fluids

Six studies investigated the effect of the administration of crystalloids on MOF in trauma patients. The majority of studies reported

crystalloid administration within the first 24 h post-injury as a risk factor for the development of MOF (36, 42, 67, 69, 70). Another study showed a trend toward a lower incidence of MOF in patients who were administered <1000 ml of fluids prior to arrival at the hospital. Two studies did not find a relation between fluids and MOF (53, 65). However, these two studies did not adjust for confounders. Pooling of data could not be performed due to difference in outcome measures. However, it is likely that crystalloid administration is an independent risk factor for MOF given that the studies, which adjusted for confounders found an association between the administration of crystalloids and MOF.

Blood products

The effect of the amount of RBCs administered on the development of MOF in trauma patients was reported in 14 studies (5, 6, 36, 41–43, 45, 46, 55, 56, 61, 66). There seems to be a dose-dependent association between MOF and transfusion, as a significant linear trend was found between the number of RBCs

Table 1 | Description of included studies; risk factors for TIC-associated MOF.

Reference	Design	Origin	Patients	N	Groups	Risk factors for MOF	Quality
Nuytinck et al. (23)	Prospective	Europe	Trauma patients	71	ARDS/MOF Non-ARDS/MOF	Plasma elastase level Complement activation	7/9
Wudel et al. (24)	Retrospective	USA	Trauma patients	92	Survivors Non-survivors	No difference	7/9
Sigurddson et al. (25)	Prospective	Asia	Critically ill patients	21	Hemorrhagic shock controls	Platelet activity and intestinal platelet sequestration	7/9
Waydhas et al. (26)	Prospective	Europe	Trauma patients	133	MOF Non-MOF	No difference in coagulopathy Platelet count <180,000/ μ L	7/9
Gando et al. (27)	Prospective	Japan	Trauma patients	58	DIC Non-DIC	DIC	6/9
Gando et al. (28)	Prospective	Japan	Trauma patients	47	DIC Non-DIC	Thrombomodulin level DIC	6/9
Sauaia et al. (29)	Retrospective	USA	Trauma patients	411	MOF Non-MOF	Colloid administration Lower platelet count Longer prothrombin time	9/9
Gando et al. (30)	Prospective	Japan	Trauma patients	136	SIRS for ≤ 2 days SIRS for ≥ 3 days Non-SIRS	SIRS ≥ 3 days Platelet counts DIC	6/9
Raeburn et al. (31)	Retrospective	USA	Trauma patients	77	Abdominal compartment syndrome (ACS)	No difference	7/9
Newell et al. (32)	Retrospective	USA	Trauma patients	1751	Normal Overweight Obese Morbidly obese	VTE	7/9
Maegele et al. (33)	Retrospective	Europe	Trauma patients	8724	Coagulopathy Non-coagulopathy	Coagulopathy	7/9
Paffrath et al. (34)	Retrospective	Europe	Trauma patients	7937	VTE Non-VTE	VTE	7/9
Nydam et al. (35)	Retrospective	USA	Trauma patients	1415	Thrombocytopenia Non-thrombocytopenia	Thrombocytopenia	8/9
Brown et al. (36)	Prospective	USA	Trauma patients	1877	Acute traumatic coagulopathy Non-acute traumatic coagulopathy Male versus female	Activation of protein C Acute coagulopathy Transfusion requirements	7/9
Kutcher et al. (37)	Prospective	USA	Trauma patients	132	High histone levels Low histone levels	High histone level	7/9
Cohen et al. (38)	Prospective	USA	Trauma patients	203	–	Higher levels of activated protein C upon admission	8/9
Cole et al. (39)	Prospective	Europe	Trauma patients	158	Infection Non-infection	PC depletion of PC and raised PAP levels	7/9
Trentzsch et al. (40)	Retrospective	Europe	Trauma patients	20,288	Male Female	No difference in coagulopathy	8/9

Table 2 | Description of included studies; risk factors for transfusion-associated MOF.

Reference	Design	Origin	Patients	N	Groups	Risk factors for MOF	Quality
Sauaia et al. (41)	Retrospective	USA	Trauma patients	394	MOF Non-MOF	>6 RBCs	8/9
Lehmann et al. (42)	Retrospective	Europe	Trauma patients	1112	MOF Non-MOF	RBC administration Crystalloids	8/9
Moore et al. (43)	Prospective	USA	Trauma patients	513	MOF Non-MOF	Blood transfusion products	8/9
Waydhas et al. (44)	RCT	Europe	Trauma patients	40	ATIII placebo	Placebo	8/10
Sauaia et al. (29)	Retrospective	USA	Trauma patients	411	MOF Non-MOF	Colloid administration Lower platelet count Longer prothrombin time	9/9
Zallen et al. (45)	Prospective	USA	Trauma patients	63	MOF Non-MOF	Number of and a Age of blood units	8/9
Cryer et al. (46)	Prospective	USA	Trauma patients	105	MOF Non-MOF	>6 RBC units	8/9
Ciesla et al. (6)	Prospective	USA	Trauma patients	1344	MOF Non-MOF	Blood products Transfusion of >6 RBCs	8/9
Frink et al. (47)	Prospective	Europe	Trauma patients	143	MOF Non-MOF	Transfusion	7/9
Bulger et al. (48)	RCT	USA	Trauma patients	209	Hypertonic fluids Ringer solution	No difference	9/10
Sperry et al. (50)	Prospective	USA	Trauma patients	415	FFP:PRBC \geq 1:1.50 FFP:PRBC \leq 1:1.51	A high FFP:PRBC ratio patients	8/9
Maegele et al. (51)	Retrospective	Europe	Trauma patients	713	RBC:FFP > 1.1 RBC:FFP 0.9–1.1 RBC:FFP < 0.9	RBC: FFP 0.9–1.1 (1:1)	8/9
Holcomb et al. (52)	Retrospective	USA	Trauma patients	467	Low plasma:RBC < 1:2 high plasma:RBC ratio > 1:2 Low platelet:RBC < 1:2 high platelet:RBC ratio > 1:2	No difference	8/9
Jastrow et al. (53)	Prospective	USA	Trauma patients	48	MOF Non-MOF	Transfusion FFPs and RBCs	7/9
Englehart et al. (54)	Prospective	USA	Trauma patients	1036	RBCs leukoreduced RBCs not leukoreduced	No difference	6/9
Dewar et al. (55)	Retrospective	USA	Trauma patients	504	MOF Non-MOF	No difference	7/9
Mahambrey et al. (56)	Retrospective	Canada	Trauma patients	260	–	RBC administration	7/9
Watson et al. (57)	Prospective	USA	Trauma patients	1175	High plasma transfusion Low plasma transfusion	FFP and cryoprecipitate	9/9
Boffard et al. (58)	RCT	Africa	Trauma patients	301	rVIIa Placebo	rVII group lower incidence MOF although not significant	8/10
Cotton et al. (59)	Prospective	USA	Trauma patients	266	Pre-massive transfusion protocol Massive transfusion protocol	Blood product administration	7/9

(Continued)

Table 2 | Continued

Reference	Design	Origin	Patients	N	Groups	Risk factors for MOF	Quality
Hauser et al. (60)	RCT	World wide	Trauma patients	573	FVIIa Placebo	A trend is observed toward decreased MOF in rFVIIa group	9/10
Paffrath et al. (34)	Retrospective	Europe	Trauma patients	7937	VTE Non-VTE	VTE	7/9
Brattstrom et al. (5)	Prospective	Europe	Trauma patients	164	–	>10 RBC units	8/9
Johnson et al. (61)	Retrospective	USA	Trauma patients	1440	MOF Non-MOF	RBC administration	8/9
Nienaber et al. (62)	Retrospective	Europe	Trauma patients	36	FFP Coagulation factor concentrates	PCC treatment associated with reduction of MOF	7/9
Perkins et al. (63)	Retrospective	USA	Trauma patients	369	Fresh whole blood Apheresis platelets	No difference	7/9
Wafaisade et al. (64)	Retrospective	Europe	Trauma patients	1362	FFP:RBC < 1:1 FFP:RBC 1:1 FFP:RBC > 1:1	No difference	7/9
Hussmann et al. (65)	Retrospective	Europe	Trauma patients	375	<1000 ml 1000–2000 ml 2001–3000 ml >3000 ml	Crystalloids <1000 ml	7/9
Brakenridge et al. (66)	Prospective	USA	Trauma patients	1366	–	>10 RBC units	7/9
Borgman et al. (67)	Retrospective	Europe	Trauma patients	2474	High FFP:RBC > 1:2 Low FFP:RBC < 1:2	No difference	8/9
Brown et al. (36)	Prospective	USA	Trauma patients	1877	Acute traumatic coagulopathy Non-acute traumatic coagulopathy	Crystalloid, RBC, and FFP administration	7/9
Innerhofer et al. (68)	Prospective	Europe	Trauma patients	144	Fibrinogen and/or prothrombin complex concentrate alone Additionally FFP	FFP administration	8/9
Minei et al. (69)	Prospective	USA	Trauma patients	916	MOF Non-MOF	FFP administration Crystalloid administration	9/9
Neal et al. (70)	Prospective	USA	Trauma patients	452	Crystalloid:RBC ratio	Crystalloid:RBC ratio >1.5:1	9/9
Duchesne et al. (71)	Retrospective	USA	Trauma patients	188	Hypertonic solution Isotonic solution	Isotonic solution	7/9

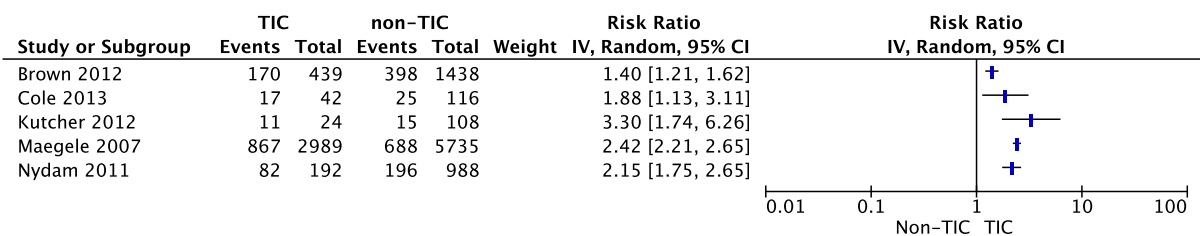


FIGURE 2 | The impact of TIC on the development of MOF. Studies have reported an association between TIC and the incidence of MOF; however, pooling of data was not possible due to substantial heterogeneity.

transfused and the incidence of MOF (43, 49). In addition, most studies reported an increased risk for MOF after administration of more than six units; however, studies could not be pooled due to differences in outcomes measures. Besides the amount of RBCs administered, the age of red blood cells of >14 days was found as an independent risk factor in four studies. Storage of RBCs for over 14 days was reported to increase the risk of MOF with an OR of 1.16 (95% CI 1.02–1.32; $P = 0.03$). The OR increased to 1.22 (95% CI 1.06–1.41; $P = 0.006$) when the RBC units were older than 21 days (45).

Eight studies investigated the effect of FFPs on the development of MOF. Two studies observed a relation between the administration of FFPs and MOF (57, 69). Other studies reported merely a trend or results were not adjusted for confounders (33, 36, 42, 50, 52, 53). When data of five observational studies were pooled for meta-analysis, there was a significant association between a high FFP:RBC ratio of $\geq 1:1$ and MOF (RR 1.11, 95% CI 1.04–1.19, **Figure 3**). Of note, studies were limited in design. The effect of platelets on the development of MOF was investigated in five studies. No significant association between platelet administration and MOF was reported in these studies (52, 53, 57, 61, 63).

Procoagulant agents

Five studies reported on the relation between MOF and the use of procoagulant agents in patients with severe hemorrhage. In an RCT with 573 patients, recombinant factor VII (rVII) significantly reduced transfusion requirements in both blunt and penetrating trauma patients and showed a trend toward a lower MOF rate in blunt trauma patients (60). Another RCT showed a lower incidence of MOF in patients treated with rVII, although these

results were not significant (58). Pooling of data from these two RCTs suggested a lower incidence of MOF in patients treated with rVII compared to placebo (RR 0.81, 95% CI 0.68–0.98, **Figure 4**).

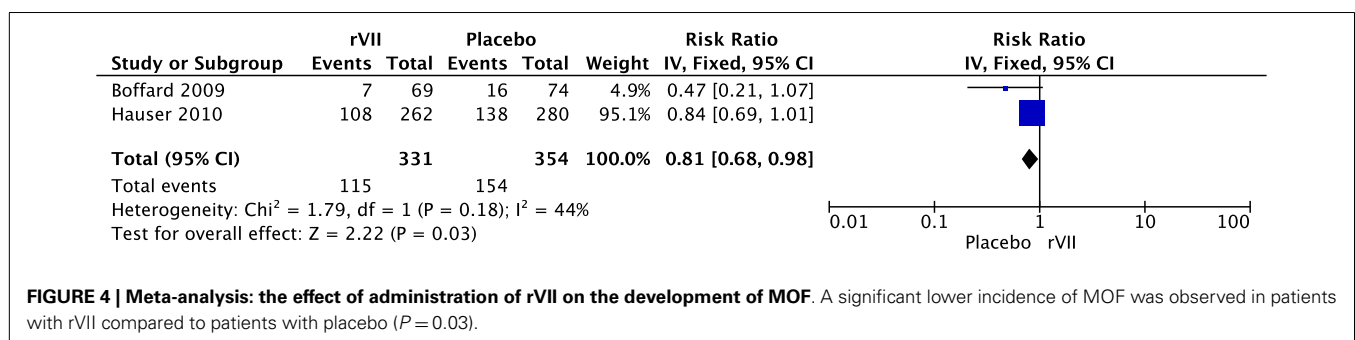
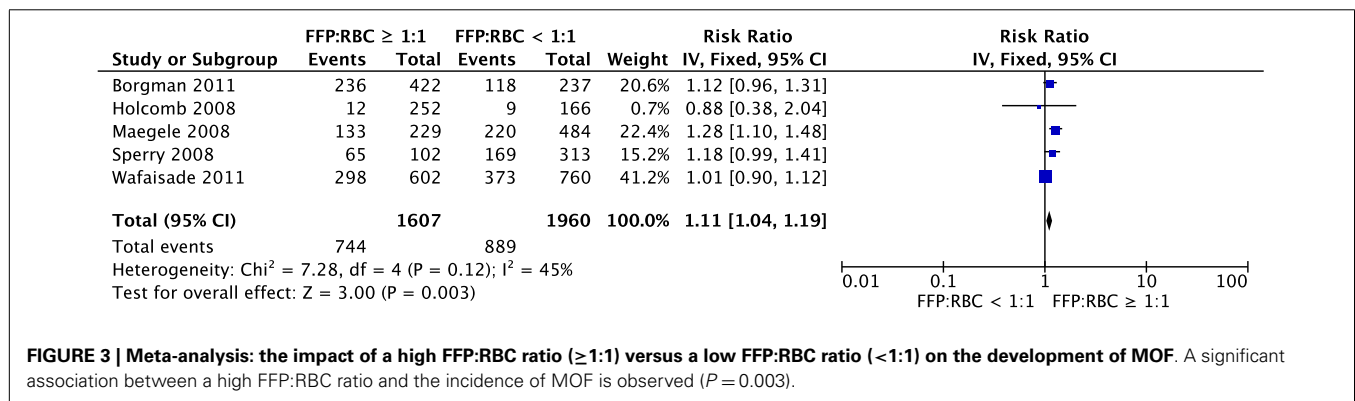
The early and high-dose administration of antithrombin (AT) significantly reduced duration of MOF, but did not reduce the incidence of MOF (44). Of note, there was no significant difference in safety profile, including thromboembolic events, between the groups. Two studies reported that prothrombin complex concentrate (PCC) administration resulted in decreased transfusion requirements with an associated significant lower frequency of MOF in severely injured trauma patients (62, 77).

In summary, the limitedly available data suggest that procoagulant agents do not contribute to a higher incidence of thromboembolic events and subsequently MOF in severe trauma patients. In fact, these agents are associated with reduced transfusion requirements and a reduced incidence of MOF.

DISCUSSION

Risk factors for TIC-associated MOF in severely injured trauma patients are early hypocoagulopathy, whereas later in the course after admission, the occurrence of thromboembolic events was associated with MOF. Risk factors for transfusion-associated MOF were the administration of fluids and red blood cell units, the age of red blood cells and an FFP:RBC ratio $\geq 1:1$. Risk factors are summarized in **Table 3**.

Hemorrhagic shock and early presence of hypocoagulopathy are risk factors for MOF in trauma patients. Subsequently, after at least 24-h after admission, thromboembolic events were reported as risk factors. Thereby, the coagulation profile associated with MOF seems to change over time. In an effort to reconcile these findings, we hypothesize that patients can transfer



from a hypocoagulable state on admission toward a hypercoagulable state later during the hospital stay, which may predispose to MOF. Immediately after tissue injury, thrombomodulin complexes and extracellular histones activate protein C, which leads to hypocoagulopathy due to the inhibition of FVa and FVII and hyperfibrinolysis (28, 37, 74, 75). Activation of protein C results in utilization of protein C. If protein C levels are consumed and patients do not recover their protein C levels, inhibition of FVa and VII will not occur, causing a hypercoagulable state. This may be followed by the formation of vascular thrombi leading to cell damage in organs and eventually MOF (Figure 5). Further studies are required to confirm this hypothesis.

Risk factors for transfusion-associated MOF are administration of crystalloids, transfusion of RBCs, the age of RBCs > 14 days and an FFP:RBC ratio $\geq 1:1$. When transfusion of fluids and blood products is inevitable a limited amount of fluid and blood products is recommended. We found that a high FFP:RBC ratio is an independent risk factor for MOF. However, since transfusion with a low FFP:RBC ratio of <1:1 is associated with a higher

mortality due to bleeding (50, 51, 79, 80), clear recommendations on the FFP:RBC ratio, with the aim to limit MOF cannot be made. In particular, due to the different scoring systems used to define MOF in the meta-analysis. Further studies on risks and benefits of blood product ratios are warranted. A possible explanation for the association between the administration of RBCs in trauma patients and MOF may be storage time. However, the use of fresh blood only is probably not feasible in exsanguinating trauma patients. Furthermore, limited data in this study suggest that procoagulant agents do not contribute to a higher incidence of thromboembolic events and subsequently MOF in severely injured trauma patients. In fact, they seem to reduce the risk of MOF, which is most likely related to a decrease in transfusion requirements. Whether the addition of procoagulant agents may decrease transfusion requirements and subsequently the development of MOF remains to be determined.

LIMITATIONS

There are several limitations to this review. The included studies have a considerable risk of bias related to design and methodology and several studies did not adjust for confounders. Also, there was a relevant heterogeneity as data were presented as mean or median, as frequencies and percentages, and as odds ratios with 95% confidence intervals. This hampered pooling of data in the meta-analysis. Pooling of data was feasible in 7 out of the 50 included studies. Additionally, we have used the Newcastle-Ottawa Scale to assess the quality of observational studies. Previous studies reported a low reliability of the scale due to differences in assessment and low agreement between reviewers, which is a limitation of the scale and subsequently of this study (81, 82). However, despite these limitations, the Cochrane Collaboration recommends the Newcastle-Ottawa scale as the most useful tool for assessing the risk of bias in non-RCTs (83). Furthermore,

Table 3 | Risk factors for TIC- and transfusion-associated MOF.

Trauma-induced coagulopathy

Hypocoagulopathy on emergency department (26, 30, 33, 35–39)
High activated protein C levels on emergency department (36, 38, 39)
High extracellular histones levels on emergency department (37)
Depleted PC levels during hospital stay (38)
Thromboembolic events, e.g., DIC and DVT during hospital stay (76, 78)

Transfusion strategy

Transfusion of RBCs, FFPs, and crystalloids within first 24 h post-injury (6, 36, 41, 43, 45, 65)
Age RBC >2 weeks (45)

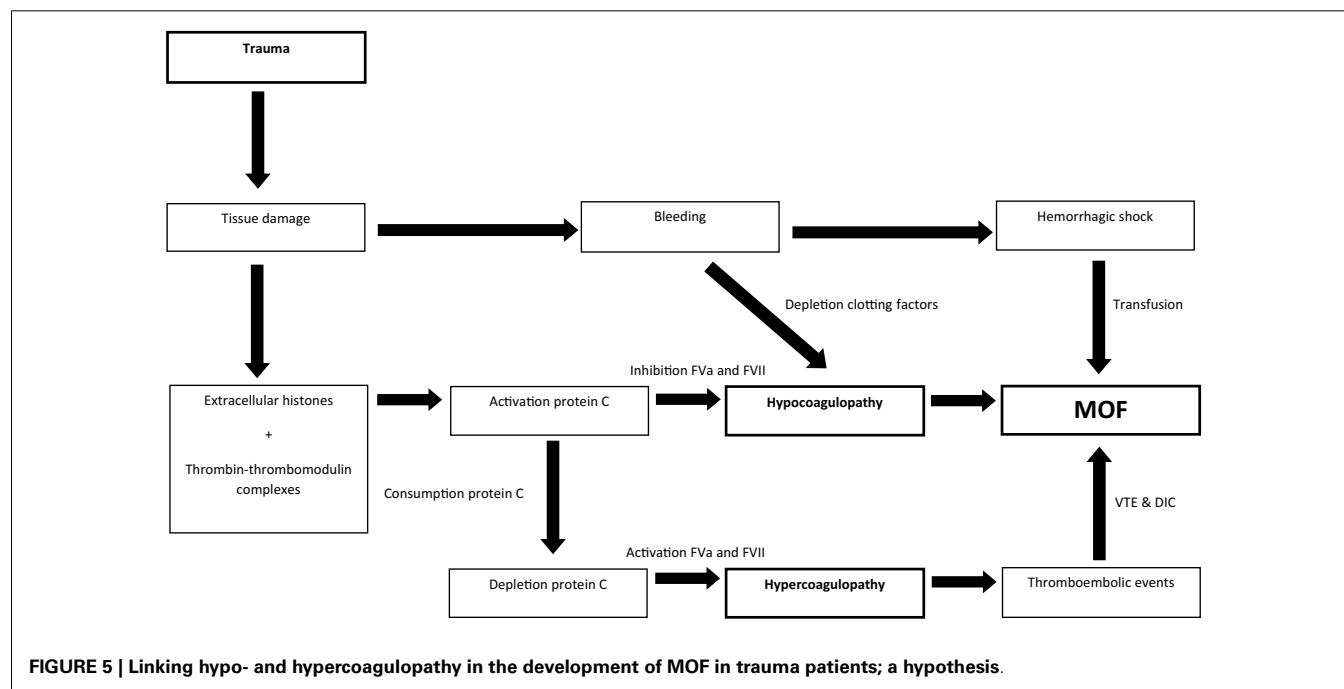


FIGURE 5 | Linking hypo- and hypercoagulopathy in the development of MOF in trauma patients; a hypothesis.

there is a lack of a uniform definition of MOF. The use of different scores of MOF hampers interpretation of the results of the meta-analyses and therefore no firm conclusions can be drawn. Additional studies are required to confirm the results of this study.

CONCLUSION

Identifying patients at high risk for MOF may guide the need for monitoring of organ failure and may provide avoidance of therapy, which can aggravate organ failure. Early hypocoagulopathy and shock are risk factors for TIC-associated MOF in severely injured trauma patients. Later in the course of trauma, a hypercoagulable state with the occurrence of thromboembolic events predisposes to MOF. Risk factors for transfusion-associated MOF include the administration of crystalloids and red blood cells and a prolonged storage time of red blood cells. However, pooling of data was hampered by heterogeneity of the study populations and outcome measures. Future prospective studies investigating TIC- and transfusion-associated risk factors on late outcome are required.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at <http://journal.frontiersin.org/article/10.3389/fmed.2015.00024/abstract>

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