neurocritical care society Neurocrit Care
DOI 10.1007/s12028-009-9281-1

ORIGINAL ARTICLE

Acute Coagulopathy in Isolated Blunt Traumatic Brain Injury

Arasch Wafaisade · Rolf Lefering · Thorsten Tjardes · Sebastian Wutzler · Christian Simanski · Thomas Paffrath · Philipp Fischer · Bertil Bouillon · Marc Maegele · Trauma Registry of DGU

Abstract

Background The role of acute coagulopathy after traumatic brain injury (TBI) on outcome has gained increasing appreciation over the recent years. This study was conducted to assess the frequency, outcome, and risk factors associated with this complication.

Patients and Methods Using the large, multi-center population-based Trauma Registry of the German Society for Trauma Surgery (TR-DGU), we retrospectively analyzed adult patients with isolated blunt TBI (intracranial $AIS_{HEAD} \geq 3$ and extracranial AIS scores <3) for the presence of acute post-traumatic coagulopathy upon emergency room (ER) arrival. Coagulopathy was defined as prothrombin time test (Quick's value) $<70\%$ and/or platelets $< 100{,}000/\mu l$.

Results From a total of 3,114 eligible patients with isolated TBI, 706 (22.7%) presented with coagulopathy upon ER arrival. Coagulopathy was associated with higher rates of craniotomies ($P = 0.02$), of single and multiple organ failure and with less intubation-free days. In surviving patients, ICU length of stay and hospital length of stay were significantly longer, if coagulopathy had been present at admission. The overall hospital mortality was 50.4% ($n = 356$) in patients with coagulopathy vs. 17.3% ($n = 417$) in non-coagulopathic patients (all $P < 0.001$). Multivariate analysis identified AIS_{HEAD} severity grade, GCS ≤ 8 at scene, the presence of hypotension at scene and/or at ER, pre-hospital i.v.-fluids $\geq$2,000 ml and age $\geq$75 years as independent risk factors for coagulopathy after TBI. Acute coagulopathy in TBI had an adjusted odds ratio for hospital mortality of 2.97 (CI_{95}: 2.30–3.85; $P < 0.001$).

Conclusion Coagulopathy upon ER admission is frequent after isolated blunt TBI and represents a powerful, independent predictor related to prognosis. Future research should aim to determine the beneficial effects of early treatment of TBI-associated coagulopathy.

Keywords Traumatic brain injury · Coagulopathy · Outcome · Mortality · Pre-hospital care

A. Wafaisade (✉) · T. Tjardes · C. Simanski · T. Paffrath · B. Bouillon · M. Maegele
Department of Trauma and Orthopedic Surgery, University of Witten/Herdecke, Cologne-Merheim Medical Center (CMMC), Ostmerheimerstr. 200, 51109 Cologne, Germany
e-mail: araschw@hotmail.com

A. Wafaisade · R. Lefering · P. Fischer · M. Maegele
Institute for Research in Operative Medicine (IFOM), University of Witten/Herdecke, Cologne-Merheim Medical Center (CMMC), Ostmerheimerstr. 200, 51109 Cologne, Germany

S. Wutzler
Department of Trauma Surgery, Hospital of the Johann Wolfgang Goethe-University, Frankfurt, Germany

Trauma Registry of DGU
Committee on Emergency Medicine, Intensive and Trauma Care (Sektion NIS) of the German Society for Trauma Surgery (DGU), Berlin, Germany

Introduction

Management of patients with traumatic brain injury (TBI) centers around preventing secondary brain injury from factors such as hypoxia, systemic hypotension, and intracranial hypertension which have been shown to have a profound effect on outcome [1, 2]. Recently, acute post-traumatic coagulopathy has been recognized as another major complication contributing to secondary brain injury and impaired outcome after TBI [3–13], but detailed

Published online: 06 October 2009

information on its frequency and potential risk factors to aggravate the detrimental effects of this coagulopathy is still lacking. This retrospective analysis was conducted to assess the overall frequency of acute post-traumatic coagulopathy in patients with isolated blunt TBI, to evaluate its potential effects on outcome and to determine risk factors contributing to acute TBI-associated coagulopathy, all by using a large multi-center population-based trauma registry.

Patients and Methods

The Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie (TR-DGU)

The TR-DGU [14] was initiated in 1993 by the German Society for Trauma Surgery (DGU) for prospective, standardized and anonymous documentation of data on severely injured patients requiring ICU treatment. Participation is voluntary and free of charge. At present, 145 trauma hospitals are participating at the TR-DGU, mainly from Germany (www.traumaregister.de). The collected data are structured in four consecutive time phases after trauma: A—pre-hospital phase including treatment and course on-scene/during transportation; B—emergency room and initial therapy until ICU admission; C—ICU; and D—discharge and list of injuries and interventions. The registry comprises detailed information on demographics, injury severity and pattern, pre- and in-hospital management, laboratory findings, time course, and outcome of each patient. Therefore, the documentation includes standardized scoring systems, e.g., the Glasgow Coma Scale (GCS) and the Abbreviated Injury Scale (AIS) [15, 16], where the grading of severity according to AIS scores ranges from 1 to 6, with increasing severity: 1 = minor, 2 = moderate, 3 = serious, 4 = severe, 5 = critical, and 6 = maximal. The TR-DGU is approved by the review board of the DGU and is in compliance with the institutional requirements of its members.

Study Population

The TR-DGU database, comprising 35,664 patients from 1993 to 2007, was retrospectively analyzed for patients with an isolated blunt (=non-penetrating) TBI. Patients <16 years of age and secondary admissions (i.e., patients admitted from other hospitals) were excluded. Patients were eligible if the documentation included complete data on demographics, injury pattern and severity, pre- and in-hospital courses (including i.v.-fluid therapy), coagulation parameters upon hospital admission, and outcome. Isolated TBI was defined as an intracranial AIS_{HEAD} score of ≥ 3 with an extracranial AIS (AIS_{BODY}) of <3, as previously described [13, 17]. Based upon these criteria a total of 3,114 patients were identified, comprising the analyzed study population.

Definition of Coagulopathy

According to our previous work [18], coagulopathy was defined by the presence of abnormal coagulation parameters upon hospital admission of the patient, i.e., prothrombin time test (Quick's value) $<70\%$ and/or platelets $<100{,}000/\mu l$ [19]. The prothrombin time (PT) test—first introduced by A. J. Quick in 1935—is either expressed in Quick-% (100% = normal) or as a PT ratio. While the international normalized ratio (INR) was introduced as a coagulation test, the PT in Quick-% is preferred by the majority of German physicians and medical institutions, where a value of $<70\%$ is equivalent to an INR > 1.3 [20–22]. Accordingly, the Trauma Registry of the DGU documents PT in Quick-%.

Outcome Evaluation

The primary outcome parameters were mortality (after 6 h, 24 h, 30 days and overall in-hospital), incidence of organ failure, Glasgow Outcome Scale (GOS), number of intubation-free days, length of ICU stay, and overall hospital stay. Organ failure was defined following the criteria of Goris et al. [23] and neurological outcome was assessed using the GOS according to Jennett et al. [24], where favorable neurological outcome was defined as a GOS of 4 (moderate disability) or 5 (good recovery) at discharge. The GOS is documented in the Trauma Registry since 2002, thus patients from 1993 to 2001 do not have a documented GOS. Intubation-free days during the first 28 days after trauma were calculated for all patients by subtracting the number of days with intubation from 28. If intubation was longer than 28 days, intubation-free days were set to zero. In the case, a patient died before day 28, intubation-free days were set to zero as well, by definition. Thus, intubation-free days range from 0 to 28 and lower values are associated with a worse outcome [25, 26]. Furthermore, lengths of stay on ICU (ICU LOS) and in hospital (HLOS) were calculated for all patients and additionally for the subgroup of surviving patients.

Statistical Analysis

Demographic and clinical data were compared between the groups using the *U*-test for continuous variables and the χ^2-test for categorical variables. Data are presented as mean with standard deviation ($\pm$SD) for continuous variables and as percentages for incidence rates. Statistical significance was set at *P*-values less than 0.05. Multivariate

analyses were performed by stepwise logistic regression with forward variable selection, first with coagulopathy as dependent variable to identify risk factors for the development of early post-traumatic coagulopathy in TBI and second with hospital mortality as dependent variable by calculating odds ratios as well as 95% confidence intervals (CI_{95}). Statistical analysis was performed applying standard statistical software (SPSS Version 15.0, SPSS, Chicago, IL, USA).

Results

From the total of 35,664 patients in the TR-DGU, 3,114 (8.7%) were eligible for further analysis. Of these 3,114 patients with isolated blunt TBI, 706 (22.7%) presented with coagulopathy upon ER admission. Table 1 summarizes the demographic, clinical, and therapeutic characteristics of patients with and without coagulopathy. In both groups patients were predominantly male (68.2 and 69.3%). TBI patients with coagulopathy were older (53 vs. 49 years) and had sustained a more severe TBI as reflected by a higher mean AIS_{HEAD} (4.5 vs. 4.2) and a lower GCS at scene (6.8 vs. 9.2; all $P < 0.001$). The degree of extracranial injuries was comparable between both groups (AIS_{BODY}: 1.0 vs. 1.0). Additionally, patients in the coagulopathy group presented with a lower systolic blood pressure both at scene (SBP: 125 vs. 134 mmHg) and upon ER arrival (125 vs. 134 mmHg; both $P < 0.001$). The mean rescue time from the estimated time of injury to arrival in the ER was longer in

Table 1 Basic demographic, clinical, and therapeutical characteristics of TBI patients with and without acute coagulopathy

N	Coagulopathy 706 (22.7%)	No coagulopathy 2,408 (77.3%)	*P*-value
Age (years; mean ± SD)	53 ± 22	49 ± 21	<0.001
Male (*n*; %)	481 (68.2)	1669 (69.3)	0.55
ISS (points; mean ± SD)	25 ± 13	21 ± 9	<0.001
AIS_{HEAD} (points; mean ± SD)	4.5 ± 0.7	4.2 ± 0.7	<0.001
AIS_{BODY} (points; mean ± SD)	1.0 ± 0.9	1.0 ± 0.9	0.16
SBP at scene (mmHg; mean ± SD)	125 ± 45	134 ± 34	<0.001
Heart rate at scene (bpm; mean ± SD)	90 ± 30	86 ± 21	<0.001
GCS at scene (points; mean ± SD)	6.8 ± 4.4	9.2 ± 4.4	<0.001
Intubation rate pre-hospital (*n*; %)	538 (76.2)	1329 (55.2)	<0.001
Time from injury to ER (min; mean ± SD)	74 ± 50	68 ± 43	<0.001
i.v. fluids pre-hospital (ml; mean ± SD)	1197 ± 1006	893 ± 704	<0.001
Crystalloids (ml; mean ± SD)	825 ± 642	716 ± 549	<0.001
Colloids (ml; mean ± SD)	355 ± 518	168 ± 314	<0.001
SBP at ER (mmHg; mean ± SD)	125 ± 35	134 ± 28	<0.001
Heart rate at ER (bpm; mean ± SD)	90 ± 24	84 ± 18	<0.001
Hemoglobin (g/dl; mean ± SD)	11.2 ± 2.7	13 ± 1.9	<0.001
Platelets (/nl; mean ± SD)	153 ± 78	221 ± 66	<0.001
Prothrombin time (Quick%; mean ± SD)	55 ± 23	93 ± 12	<0.001
Base excess (mmol/l; mean ± SD)	−4.1 ± 5.6	−1.9 ± 4.6	<0.001
Epidural hematoma (*n*; %)	85 (12.0)	361 (15.0)	0.05
Subdural hematoma (*n*; %)	308 (43.6)	885 (36.8)	0.001
Subarachnoid hematoma (*n*; %)	44 (6.2)	192 (8.0)	0.12
Intracerebral hematoma/contusion (*n*; %)	168 (23.8)	670 (27.8)	0.03
Brain stem injury (*n*; %)	25 (3.5)	86 (3.6)	0.97
Craniotomy (*n*; %)	207 (29.3)	600 (24.9)	0.02
Blood product transfusion[a] (*n*; %)	163 (23.0)	183 (7.6)	<0.001
pRBC units[a] (*n*; mean ± SD)	1.3 ± 3.4	0.3 ± 0.02	<0.001
FFP units[a] (*n*; mean ± SD)	0.6 ± 0.1	0.1 ± 0.02	<0.001

AIS abbreviated injury scale; *bpm* beats per minute; *ER* emergency room; *FFP* fresh frozen plasma; *GCS* Glasgow Coma Scale; *ICU* intensive care unit; *ISS* injury severity score; *pRBC* packed red blood cells; *SD* standard deviation; *SBP* systolic blood pressure

[a] Blood products transfused between ER arrival and ICU admission

patients with coagulopathy (74 vs. 68 min; $P < 0.001$) and the pre-hospital intubation rate was higher in the coagulopathy group (76.2 vs. 55.2%; $P < 0.001$).

The incidence of coagulopathy increased with increasing injury severity, as coagulopathy rates in AIS_{HEAD} subgroups 3, 4, 5, and 6 were 14.0% ($n = 72$), 17.3% ($n = 242$), 31.6% ($n = 360$), and 52.5% ($n = 32$), respectively ($P < 0.001$). TBI patients with coagulopathy had received higher amounts of i.v.-fluids prior to hospital admission (1,197 ± 1,006 ml; crystalloid–colloid-ratio 2.3:1) than non-coagulopathic patients (893 ± 704 ml, $P < 0.001$; crystalloid–colloid-ratio 4.3:1, $P < 0.001$). Figure 1 displays the association between the presence of coagulopathy, injury severity, and pre-hospital i.v.-fluid therapy.

Upon ER arrival, physiologic and laboratory values were more deranged in patients with coagulopathy, for example hemoglobin (11.2 vs. 13 g/dl), base excess (−4.1 vs. −1.9 mmol/l) and heart rate (90 vs. 84 beats per minute; all $P < 0.001$). Figure 2 depicts the association between the presence of hypotension (defined as SBP ≤ 90 mmHg) at scene, upon ER admission and at both time points and the presence of coagulopathy.

Coagulopathy was predominantly associated with subdural hematoma (43.6 vs. 36.8%; $P = 0.001$), with a higher frequency of craniotomies (29.3 vs. 24.9%; $P = 0.02$) and with significantly increased rates and amounts of transfused blood products (Table 1).

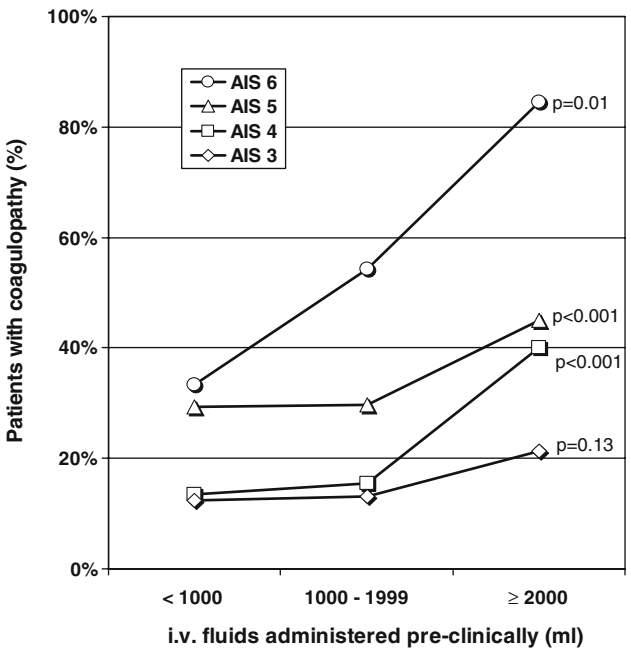

Fig. 1 Association between incidence of TBI-associated coagulopathy and pre-hospital i.v.-fluid therapy in respective AIS_{HEAD}-subgroups

The presence of acute coagulopathy after TBI was associated with increased morbidity and mortality. Table 2 lists outcome parameters for both patients with and without coagulopathy. Patients in the coagulopathy group had significantly higher incidences of single (SOF) and multiple organ failure (MOF) and less intubation-free days. Mortality rates were significantly higher in this group at all time points. The overall hospital mortality totaled 50.4% ($n = 356$) in the coagulopathy group in contrast to 17.3% ($n = 417$) among the patients without coagulopathy ($P < 0.001$). In surviving patients, ICU length of stay (LOS) and hospital length of stay (HLOS) were significantly longer if acute coagulopathy had been present (ICU LOS: 14 vs. 10 days; HLOS: 25 vs. 20 days; both $P < 0.001$).

The outcome parameters (intubation-free days; incidence of MOF; GOS; mortality) were further stratified according to AIS_{HEAD} severity grades (Fig. 3), demonstrating that outcomes worsened with increasing TBI severity but were generally impaired for patients with coagulopathy across all severity grades.

Multivariate logistic regression analysis identified AIS_{HEAD} severity grade, GCS ≤ 8 at scene, the presence of hypotension at scene and/or at ER (defined as SBP ≤ 90 mmHg), the amount of pre-hospital i.v.-fluids ≥2,000 ml and an age ≥75 years as independent risk factors for coagulopathy following TBI (Table 3). A second multivariate analysis was performed to assess the impact of TBI-associated coagulopathy on hospital mortality. After adjustment for AIS_{HEAD} severity grade, GCS, hypotension at scene or at ER (SBP ≤ 90 mmHg) and age, coagulopathy in TBI carried an odds ratio of 2.97 (CI_{95}: 2.30–3.85; $P < 0.001$) in predicting hospital mortality.

Discussion

The present study was conducted to assess the overall frequency of acute post-traumatic coagulopathy upon hospital admission in patients with isolated blunt TBI, to evaluate the potential impact of acute coagulopathy on outcome and to determine contributing risk factors.

Previously, coagulopathy after trauma was considered to be caused primarily by the loss and dilution of clotting factors following volume therapy. However, the intrinsic hemostatic regulatory mechanisms involve a complex principal balance between clot formation and breakdown. Following endothelial injury, clot initiation occurs through vasoconstriction, platelet plug creation, fibrin mesh formation, and lysis [27]. Accordingly, recent research provides evidence that coagulopathy after traumatic injury is a complex process involving all components of the hemostatic system. Current literature suggests six key

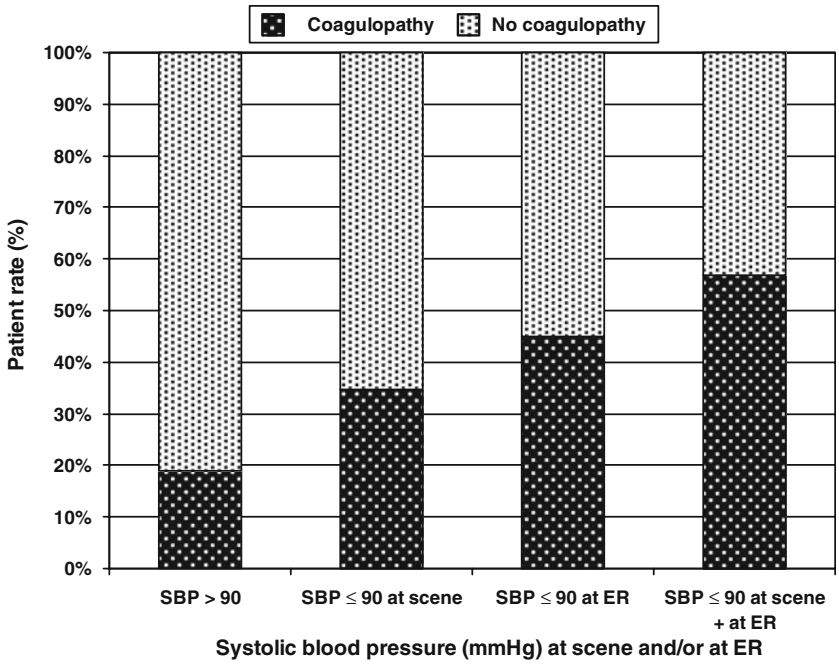

Fig. 2 Incidence of TBI-associated coagulopathy in patient groups according to presence of hypotension (defined as systolic blood pressure (SBP) ≤90 mmHg); *ER* emergency room; $P < 0.001$

Table 2 Outcome of TBI patients with and without acute coagulopathy

	Coagulopathy 706 (22.7%)	No coagulopathy 2,408 (77.3%)	*P*-value
Single organ failure (*n*; %)	429 (60.7)	932 (38.7)	<0.001
Multiple organ failure (*n*; %)	252 (35.7)	467 (19.4)	<0.001
Intubation-free days (days; mean ± SD)	11 ± 13	20 ± 12	<0.001
ICU LOS (days; mean ± SD)	9 ± 13	9 ± 11	0.99
Survivors ICU LOS (days; mean ± SD); $n = 2{,}320$	14 ± 15	10 ± 12	<0.001
HLOS (days; mean ± SD)	15 ± 22	18 ± 20	<0.001
Survivors HLOS (days; mean ± SD); $n = 2{,}298$	25 ± 26	20 ± 21	<0.001
Discharge GOS 4–5 (*n*; %); $n = 2{,}104$	155 (31.8)	1007 (62.3)	<0.001
6-h mortality (*n*; %)	104 (14.7)	32 (1.3)	<0.001
24-h mortality (*n*; %)	184 (26.1)	105 (4.4)	<0.001
30-day mortality (*n*; %)	347 (49.2)	407 (16.9)	<0.001
In-hospital mortality overall (*n*; %)	356 (50.4)	417 (17.3)	<0.001

GOS Glasgow Outcome Scale (Results of GOS based on 2,104 patients with documented and complete GOS; the GOS is documented in the Trauma Registry since 2002, therefore patients from 1993 to 2001 do not have a documented GOS); *ICU* intensive care unit; *(H)LOS* (hospital) length of stay; *SD* standard deviation

initiators contributing to traumatic coagulopathy: tissue trauma, shock, hemodilution, hypothermia, acidemia, and inflammation [28]. At the same time each factor itself may have the potential to substantially exacerbate the other [29], leading to aggravated hemorrhage and eventually to death. These recent findings have resulted in a new appreciation of trauma-associated coagulopathy.

In the present investigation, nearly one out of four TBI patients studied had abnormal coagulation parameters upon ER admission. The incidence of coagulation disorders after TBI has been reported to vary between 10 and more than 90% [4, 12]. This variation has mainly been attributed to (i) the differences in study designs, (ii) the diversity of injury severities among reported studies, (iii) different time points for testing of coagulation parameters, and (iv) the absence of a universally recognized definition of coagulopathy. However, recent prospective studies with sufficient patient numbers reported incidence rates for coagulopathy in TBI between 17% [22] and 34% [13].

A growing body of literature suggests an association between the presence of early coagulopathy after TBI and impaired outcome [3–13]. In the present study, acute

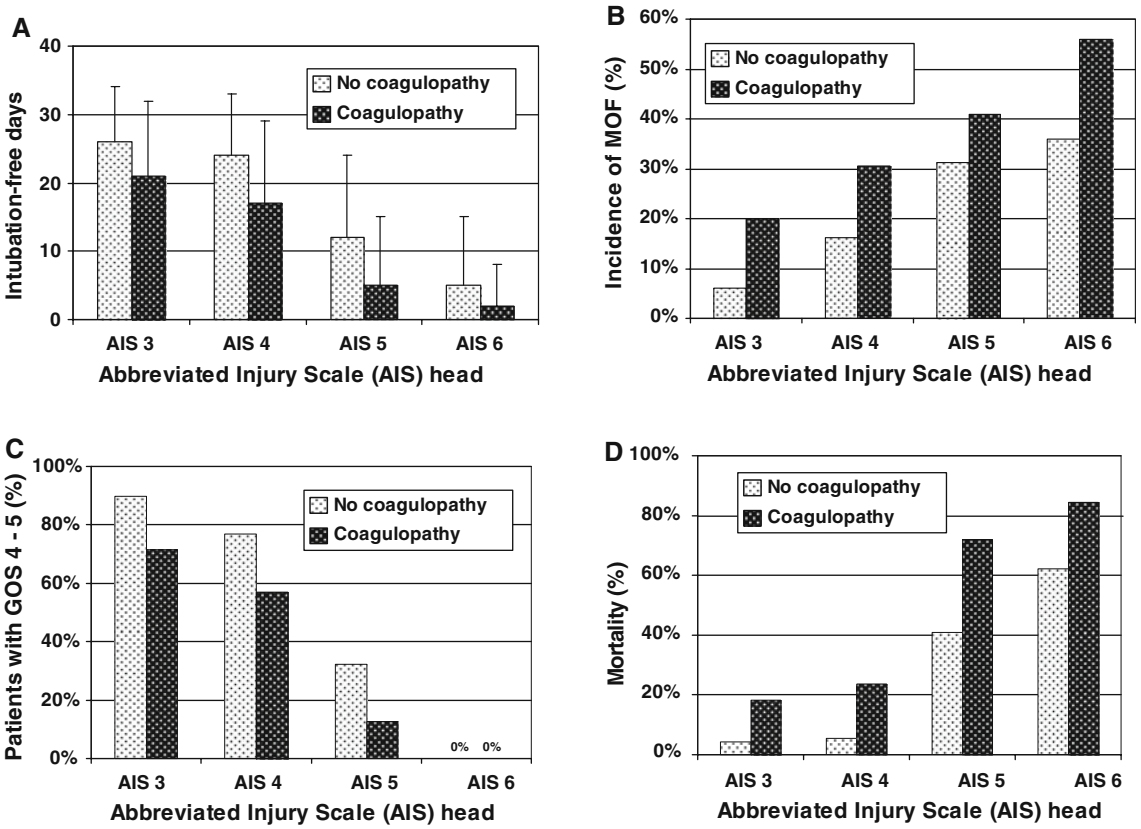

Fig. 3 Outcome in TBI patients with and without acute coagulopathy in respective AIS_{HEAD}-subgroups. **a** Intubation-free days; **b** Incidence of multiple organ failure (MOF); **c** Patient rate discharged with a favorable GOS of 4 or 5 (Results of GOS based on 2,104 patients with documented and complete GOS; the GOS is documented in the Trauma Registry since 2002, therefore patients from 1993 to 2001 do not have a documented GOS.); **d** Mortality. All outcomes were consistently impaired among TBI patients with coagulopathy (all $P < 0.001$)

TBI-associated coagulopathy was a significant independent predictor of an unfavorable outcome with respect to survival, not only in the acute phase after injury but also during the later sequelae. While we report a threefold increase in overall in-hospital mortality, this rate may increase up to ten times as shown in a recent prospective clinical trial [13]. The higher rate of single (SOF) and multiple organ failure (MOF) in the presence of acute posttraumatic coagulopathy corresponds to previous studies in which coagulation disorders after TBI were linked to ongoing hemorrhage, thromboembolic infarction, and organ necrosis [30, 31]. These events may also contribute to a negative neurological prognosis [6]. The present results emphasize the association of coagulopathy with impaired neurological outcome as reflected by GOS at discharge. For the surviving patients ICU and hospital lengths of stay were significantly longer when early posttraumatic coagulopathy was present upon ER arrival. Similar results have been published previously [3, 13]. We also observed less intubation-free days in patients with coagulopathy, a surrogate implicating that this group had a more complicated hospital course.

To date, only few studies have investigated the predictive value of acute coagulopathy in TBI with logistic regression models adjusted for other predictors [8, 10, 13], confirming that coagulation parameters predict poor outcome independently of other variables. Recently, the prothrombin time has been identified as a powerful independent prognostic factor after TBI [6]. In this study, odds ratios for mortality were adjusted for hypotension which appears to be mandatory given the high prognostic value of low blood pressure as shown in other studies [1, 6, 9, 32, 33]. It is remarkable that in our study the adjusted risk for hospital mortality in patients with coagulopathy after TBI was three times higher than in non-coagulopathic patients.

Stepwise logistic regression identified AIS_{HEAD} scores followed by GCS scores at scene as the most important predictors for the development of acute coagulopathy after TBI. These results correspond to prior investigations demonstrating that the magnitude of brain trauma plays an important role for the development of coagulation disorders after TBI [5, 8, 13, 32, 34]. GCS has been applied previously by several investigators to define the severity of TBI [3, 8, 9, 32]. However, in this context it has to be

Table 3 Independent risk factors for development of acute coagulopathy in TBI (multivariate analysis)

Risk factor	Odds ratio (CI_{95})	*P*-value
AIS_{HEAD}		
AIS 4	1.36 (0.99–1.88)	0.057
AIS 5	2.25 (1.63–3.10)	<0.001
AIS 6	4.04 (2.14–7.63)	<0.001
GCS ≤ 8 at scene	1.71 (1.38–2.12)	<0.001
SBP ≤ 90 mmHG at scene	1.74 (1.30–2.32)	<0.001
SBP ≤ 90 mmHG at ER	2.34 (1.64–3.34)	<0.001
i.v. fluids pre-hospital		
2,000–2,999 ml	2.15 (1.63–2.84)	<0.001
≥3,000 ml	3.48 (2.13–5.68)	<0.001
Age		
65–74 years	1.31 (0.99–1.73)	0.063
≥75 years	2.30 (1.79–2.96)	<0.001

The logistic regression model was started with eight variables, two variables were excluded by the model (sex; subdural hematoma). *AIS* abbreviated injury scale; *GCS* Glasgow Coma Scale; *SBP* systolic blood pressure

considered carefully that the association between low GCS and coagulopathy we could observe in our study might also indicate that patients with a coagulation disorder are at higher risk for neurological deterioration and decreased GCS. In the present study, it was also observed that the frequency of coagulopathy increased with increasing injury severity as reflected by AIS_{HEAD} scores. One hypothesis is related to the TBI-induced release of tissue factor (TF) into the systemic circulation leading to the activation of the coagulation cascade by instigating the extrinsic pathway [12, 17, 35]. Further processes being activated in this context include fibrinolysis, complement [31], and inflammatory cascades [36]. Coagulopathy invokes on the one hand consumption of coagulation factors further aggravating clinically significant bleeding, and on the other hand diffuse intravascular activation of coagulation, leading to fibrin deposition and thromboembolic ischemia [12, 28]. Thus, acute post-traumatic coagulopathy is not only a result from injury, but may also trigger secondary injury. Prior investigations have reported that the presence of coagulopathy upon ER admission is associated with delayed cerebral injury, progression of intracranial hemorrhages and impaired outcome [7, 11, 12, 17].

Hypotension on admission has previously been described as a further independent risk factor for coagulopathy [13]. In the present study, the presence of hypotension at scene and/or at ER and the amount of i.v.-fluids administered during the pre-hospital phase of care were independently associated with occurrence of coagulopathy after TBI. This observation reflects once more the complexity of the underlying pathomechanisms of TBI-associated coagulopathy. On the one hand, i.v.-fluids are administered to support cardiovascular performance in an effort to maintain adequate cerebral perfusion and to limit secondary brain injury [1, 33]. Hypotension has recently been identified as another principle driver of coagulopathy possibly via the activation of the protein-C-pathway [28, 37]. On the other hand, concerns are raised that aggressive fluid resuscitation can lead to hemodilution including dilution of coagulation factors, subsequently exacerbating hemostatic disorders [28, 33, 36, 38].

The age ≥75 years was calculated as a further independent predictor for TBI-associated coagulopathy, which corresponds to previous reports [7]. However, the authors are aware that a higher frequency of pre-existing diseases or anticoagulant medication in this group of patients may partially be responsible for this observation. Data-collection on pre-existing diseases or medication has been added to the TR-DGU just recently, and exclusion of patients without this information would have reduced our study population substantially. Still, even in prospective studies some investigators have excluded these patients [17, 22], while others have not [13], latters probably in an attempt to assess the role of coagulation disorders on outcome regardless of its origin.

Several studies reported coagulopathy to occur most frequently with acute subdural hematoma (SDH), subarachnoid hemorrhage, or parenchymal contusions [5, 13]. In our study population the incidence of SDH was significantly higher in coagulopathic patients, but none of the different types of intracranial pathologies were calculated to be independently associated with coagulopathy after TBI.

TBI-associated coagulopathy may be amenable to early therapeutical approaches, as adequate and prompt intervention may prevent secondary complications and poorer outcome. Hence, investigating the beneficial effects of pre- and in-hospital treatment protocols in TBI with respect to effects on coagulation should be a priority for future research.

The present study has certain limitations. First, the partial thromboplastin time (PTT) was not available in all datasets and could therefore not be used to define patients with coagulopathy. Second, other laboratory values, which might be of interest with respect to coagulation (e.g., fibrinogen, protein C) are not documented at all in the Trauma Registry. The data is furthermore limited as the TR-DGU has been designed to register severely and/or multiply injured patients requiring ICU admission only. The number of patients studied with an isolated AIS_{HEAD} 3 appears relatively low, as this subgroup is considered to be injured relevantly but not severely and thus is included in the registry less frequently by on-site hospital staff in charge. Another issue refers to the unequal sample size of the groups studied which may limit the interpretation of the

obtained results. Despite the well-known importance of hypothermia as a major contributing factor for coagulopathy [28], body temperature is documented only very inconsistently in our registry. The exclusion of patients with missing data would have substantially reduced our study population to a small fraction. Furthermore, the evaluation of intubation-free days has the limitation that patients which were subjected to tracheostomy cannot be abstracted from the database. Finally, we conducted a retrospective analysis and only associations but no causalities can be ascribed from the given data.

Conclusion

Coagulopathy upon hospital admission is a frequent finding in adult patients after isolated blunt TBI and represents a powerful and independent predictor related to prognosis. Independent risk factors for coagulopathy in isolated TBI are AIS_{HEAD} severity grade, GCS ≤ 8, hypotension at scene and/or at ER, pre-hospital i.v.-fluids $\geq$2,000 ml and age $\geq$75 years. Prospective clinical trials should be conducted to determine the beneficial effects of early treatment of TBI-associated coagulopathy.

References

1. Dutton RP, McCunn M. Traumatic brain injury. Curr Opin Crit Care. 2003;9(6):503–9.
2. Elf K, Nilsson P, Enblad P. Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care. Crit Care Med. 2002;30(9):2129–34.
3. Carrick MM, Tyroch AH, Youens CA, Handley T. Subsequent development of thrombocytopenia and coagulopathy in moderate and severe head injury: support for serial laboratory examination. J Trauma. 2005;58(4):725–9.
4. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. Acta Neurochir (Wien). 2008;150(2):165–75.
5. Kumura E, Sato M, Fukuda A, Takemoto Y, Tanaka S, Kohama A. Coagulation disorders following acute head injury. Acta Neurochir (Wien). 1987;85(1–2):23–8.
6. Murray GD, Butcher I, McHugh GS, Lu J, Mushkudiani NA, Maas AI, et al. Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24(2):329–37.
7. Oertel M, Kelly DF, McArthur D, Boscardin WJ, Glenn TC, Lee JH, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. J Neurosurg. 2002;96(1):109–16.
8. Olson JD, Kaufman HH, Moake J, O'Gorman TW, Hoots K, Wagner K, et al. The incidence and significance of hemostatic abnormalities in patients with head injuries. Neurosurgery. 1989;24(6):825–32.
9. Piek J, Chesnut RM, Marshall LF, Berkum-Clark M, Klauber MR, Blunt BA, et al. Extracranial complications of severe head injury. J Neurosurg. 1992;77(6):901–7.
10. Selladurai BM, Vickneswaran M, Duraisamy S, Atan M. Coagulopathy in acute head injury—a study of its role as a prognostic indicator. Br J Neurosurg. 1997;11(5):398–404.
11. Stein SC, Young GS, Talucci RC, Greenbaum BH, Ross SE. Delayed brain injury after head trauma: significance of coagulopathy. Neurosurgery. 1992;30(2):160–5.
12. Stein SC, Smith DH. Coagulopathy in traumatic brain injury. Neurocrit Care. 2004;1(4):479–88.
13. Talving P, Benfield R, Hadjizacharia P, Inaba K, Chan LS, Demetriades D. Coagulopathy in severe traumatic brain injury: a prospective study. J Trauma. 2009;66(1):55–61.
14. Scoring study committee of the German Society of Trauma Surgery. Trauma register of the German Society of Trauma Surgery. Unfallchirurg. 1994;97(4):230–7.
15. Association for the Advancement of Automotive Medicine. The Abbreviated Injury Scale (AIS) 1990 Revision. Barrington, Illinois: Association for the Advancement of Automotive Medicine; 1990.
16. Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma. 1974;14(3):187–96.
17. Halpern CH, Reilly PM, Turtz AR, Stein SC. Traumatic coagulopathy: the effect of brain injury. J Neurotrauma. 2008;25(8):997–1001.
18. Maegele M, Lefering R, Yucel N, Tjardes T, Rixen D, Paffrath T, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury. 2007;38(3):298–304.
19. Thomas L. Labor und Diagnose: Indikation und Bewertung von Laborbefunden für die medizinische Diagnostik, vol. 5. erweiterte Auflage: TH-Books; 2000.
20. Lutze G. Useful facts about coagulation. Mannheim: Roche Diagnostics GmbH, (data on file).
21. Wagner C, Dati F. Thromboplastinzeit. In: Thomas L, editor. Labor und Diagnose. Frankfurt: TH-Books Verlagsgesellschaft; 2000. p. 613–6.
22. Zehtabchi S, Soghoian S, Liu Y, Carmody K, Shah L, Whittaker B, et al. The association of coagulopathy and traumatic brain injury in patients with isolated head injury. Resuscitation. 2008;76(1):52–6.
23. Goris RJ, te Boekhorst TP, Nuytinck JK, Gimbrere JS. Multiple-organ failure. Generalized autodestructive inflammation? Arch Surg. 1985;120(10):1109–15.
24. Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. J Neurol Neurosurg Psychiatry. 1981;44(4):285–93.
25. Lefering R, Paffrath T, Linker R, Bouillon B, Neugebauer EA. Head injury and outcome—what influence do concomitant injuries have? J Trauma. 2008;65(5):1036–43.
26. Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med. 2002;30(8):1772–7.
27. Kauvar DS, Wade CE. The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. Crit Care. 2005;9(Suppl 5):S1–9.
28. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma. 2008;65(4):748–54.
29. Schreiber MA. Damage control surgery. Crit Care Clin. 2004;20(1):101–18.
30. Kaufman HH, Hui KS, Mattson JC, Borit A, Childs TL, Hoots WK, et al. Clinicopathological correlations of disseminated intravascular coagulation in patients with head injury. Neurosurgery. 1984;15(1):34–42.

31. Levi M, ten Cate H. Disseminated intravascular coagulation. N Engl J Med. 1999;341(8):586–92.
32. Affonseca CA, Carvalho LF, Guerra SD, Ferreira AR, Goulart EM. Coagulation disorder in children and adolescents with moderate to severe traumatic brain injury. J Pediatr (Rio J). 2007;83(3):274–82.
33. Badjatia N, Carney N, Crocco TJ, Fallat ME, Hennes HM, Jagoda AS, et al. Guidelines for prehospital management of traumatic brain injury 2nd edition. Prehosp Emerg Care. 2008;12(Suppl 1): S1–52.
34. Scherer RU, Spangenberg P. Procoagulant activity in patients with isolated severe head trauma. Crit Care Med. 1998; 26(1):149–56.
35. Pathak A, Dutta S, Marwaha N, Singh D, Varma N, Mathuriya SN. Change in tissue thromboplastin content of brain following trauma. Neurol India. 2005;53(2):178–82.
36. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003;54(6):1127–30.
37. Cohen MJ, Brohi K, Ganter MT, Manley GT, Mackersie RC, Pittet JF. Early coagulopathy after traumatic brain injury: the role of hypoperfusion and the protein C pathway. J Trauma. 2007; 63(6):1254–61.
38. Coats TJ, Brazil E, Heron M, MacCallum PK. Impairment of coagulation by commonly used resuscitation fluids in human volunteers. Emerg Med J. 2006;23(11):846–9.