Coagulopathy on the first postoperative day predicting the long-term survival of traumatic brain injury patients

CURRENT STATUS: POSTED

Wenxing Cui
Xi'an Tangdu Hospital of No4 Military Medical University

Shunnan Ge
Xi'an Tangdu Hospital of No4 Military Medical University

Yingwu Shi
Xi'an Tangdu Hospital of No4 Military Medical University

Xun Wu
Xi'an Tangdu Hospital of No4 Military Medical University

Jianing Luo
Xi'an Tangdu Hospital of No4 Military Medical University

Dayun Feng
Xi'an Tangdu Hospital of No4 Military Medical University

Gang Zhu
Xi'an Tangdu Hospital of No4 Military Medical University

Bao Wang
Xi'an Tangdu Hospital of No4 Military Medical University

Hao Guo
Xi'an Tangdu Hospital of No4 Military Medical University

Haixiao Liu
Xi'an Tangdu Hospital of No4 Military Medical University

Yan Qu yanqu0123@fmmu.edu.cn
Xi'an Tangdu Hospital of No4 Military Medical University

Corresponding Author

DOI:
10.21203/rs.2.23641/v1

SUBJECT AREAS
Keywords
traumatic brain injury, survival analysis, perioperative coagulopathy, fluid management
Abstract

Objective: The purpose of this study was to identify the relationship between coagulopathy during the perioperative period (before the operation and on the first day after the operation) and the long-term survival of TBI patients undergoing surgery, as well as to explore the predisposing risk factors that may cause perioperative coagulopathy.

Methods: This retrospective study included 447 TBI patients who underwent surgery from January 1, 2015 to April 25, 2019. Clinical parameters, including patient demographic characteristics, biochemical tests, perioperative coagulation function tests (before the operation and on the first day after the operation) and intraoperative factors were collected. Log-rank univariate analysis and Cox regression models were conducted to assess the relationship between perioperative coagulopathy and the long-term survival of TBI patients. Furthermore, univariate and multivariate analyses were performed to identify the underlying risk factors for perioperative coagulopathy.

Results: Multivariate Cox regression analysis identified age, AIS\textsubscript{head} = 5, GCS ≤ 8, systolic pressure at admission < 90 mmHg and postoperative coagulopathy (all P < 0.05) as independent risk factors for survival following TBI; we were the first to identify postoperative coagulopathy as an independent risk factor. According to multivariate logistic regression analysis, for the first time, abnormal ALT and RBC at admission, preoperative coagulopathy, infusion of colloidal solution > 1100 mL and intraoperative bleeding > 950 mL (all P < 0.005) were identified as independent risk factors for postoperative coagulation following surgery after TBI.

Conclusions: Those who suffered from postoperative coagulopathy due to TBI had a higher hazard for poor prognosis than those who did not. Closer attention should be paid to postoperative coagulopathy and more emphasis should be placed on managing the
underlying risk factors.

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide, and it represents a global health concern and financial burden [1, 2]. The main causes of early death in trauma victims are acidosis, hypothermia and coagulopathy, which are related to each other and influence each other. Thus, this vicious circle is often referred to as the "trauma triangle of death" [3, 4]. Trauma-induced coagulopathy manifests as a state of hypercoagulopathy trending towards thrombosis [5] and a state of hypocoagulopathy with progressive intracranial hemorrhage and increased systemic bleeding [6, 7].

There are many studies continuously proving that trauma-induced coagulopathy is common in traumatic brain injury patients [8-10] and the incidence of coagulation disorders has great heterogeneity, ranging from 7-54% [11, 12]. Reasons that cause this variation include the different techniques and definitions used, the heterogeneity of the patients and the various testing times [13]. Secondary coagulopathy after traumatic brain injury represent an important factor for unfavorable prognosis [14, 15], resulting in a nine-fold higher risk of death and a 30-fold higher risk of poor prognosis than in TBI patients without secondary coagulation disorder [7, 9, 16]. Mortality in TBI patients with coagulopathy is also highly heterogeneous, ranging from 22-66% [17, 18]. TBI patients with coagulopathy tend to suffer from delayed or progressive intracranial hemorrhage, as well as from microvascular thrombosis [19, 20].

Many retrospective and observational studies have focused on coagulation upon admission or the presence of any coagulation disorders during the whole period of hospitalization [21, 22]. A multicenter study described the course of coagulopathy in patients with isolated TBI, and associated it with CT characteristics and outcomes [15]. The previous
study mostly focused on the coagulopathy on admission, while the association between coagulopathy in perioperative period and long-term survival of TBI patients has not been explored. It is important to explore this relationship because many TBI patients require surgical treatment, and it has been well established that the surgical intervention have an impact on the coagulation functions. We therefore investigated for the first time whether coagulopathy during the perioperative period, with the use of coagulation function tests performed before the operation and on the first day after the operation, was related to the long-term survival of these patients. Furthermore, we investigated the predisposing risk factors that may cause coagulopathy in the perioperative period, to the extent that these risk factors could be controlled and managed for avoiding coagulopathy.

**Materials And Methods**

The clinical data of 447 TBI patients were retrospectively collected from January 1, 2015 to April 25, 2019 in the Second Affiliated Hospital of the Fourth Military Medical University. We included patients who recorded an intracranial injury as the main diagnosis or the coexisting diagnoses upon admission. Intracranial injuries were identified by WHO ICD-11 codes from NA07.0 to NA07.9. The inclusion criteria were any patients with mild, moderate, or severe TBI who entered the operating room for surgery, including for decompressive craniectomy and the evacuation of an intracranial hematoma. Other inclusion criteria were that the interval from injury to admission was less than 24 hours, an absence of other severe extracranial injuries, and an extracranial Abbreviated Injury Scale (AIS) score < 3. TBI patients who did not undergo surgery or who did not survive before undergoing any surgery were excluded from the study. TBI patients who had hemorrhagic or ischemic cerebrovascular disease within half a year or who had other systemic diseases, such as uremia, cirrhosis, or malignant tumors were also excluded. The primary variable of interest was coagulation disturbance during the perioperative period.
phase. We recorded the coagulation function before the operation and on the first day after the operation. Coagulopathy was defined as an aPTT > 40 sec and/or an INR > 1.2, and/or a platelet count < 100 × 10^9 per liter [23, 24]. Patient demographic characteristics and biochemical tests were also retrospectively adjusted for the evaluation of the relationship between perioperative coagulation and outcome. The demographic data collected included age(< 45 years, 45–60 years, and > 60 years), gender, admission AIS (head), admission Glasgow Coma Scale (GCS), which was categorized as moderate (GCS 9–13) or severe (GCS 3–8), pupil reaction at admission, systolic pressure at admission, multiple traumas, and CT findings of midline shift and subarachnoid hemorrhage. The patient biochemical tests upon admission included serum glucose(GLU), hemoglobin[GB], aspartate aminotransferase(AST), alanine aminotransferase(ALT), blood urea nitrogen(BUN), K^+ , Na^+, Cl^−, Ca^{2+} and red blood cells (RBCs) at admission. Systolic pressure < 90 mmHg, GLU > 151 mg/dL, GB < 120 g/L, AST ≥ 40 U/L, ALT ≥ 40 U/L, BUN > 7.1 × 10^{12}/L, K^+ < 3.5 mmol/L or > 5.5 mmol, Na^+ < 135 mmol/L or > 145 mmol/L, Cl^− <95 mmol/L or > 105 mmol/L, Ca^{2+} < 2.25 mmol/L or > 2.75 mmol/L, and RBCs(men > 5.5 × 10^{12}/L or < 4.0 × 10^{12}/L, and women > 5.0 × 10^{12}/L or < 3.5 × 10^{12}/L) were regarded as abnormal values.

Because we found that the presence of postoperative coagulation disorders was closely related to long-term survival, we reviewed the intraoperative factors in the next step, including the preoperative systolic pressure, preoperative shock index, infusion of crystalloid solution and colloidal solution, ratio of infusion plasma to RBCs, perioperative-bleeding, net fluid input, total surgery time and surgical approach. The net fluid input was calculated as the sum of the crystalloid solution and colloid solution and infusion of blood products, and was then subtracted from the amount of intraoperative blood loss and urine.
The shock index was categorized as normal (< 1.0), mild (1.0-1.5), moderate or severe shock (> 1.5). The crystalloid solution, colloidal solution, intraoperative-bleeding, net fluid input, and total surgery time were analyzed as categorical variables, which were classified by using ROC curve analysis based on postoperative coagulation (Supplementary Figs. 1–5).

Follow-up was conducted by telephone or inpatient or outpatient review, and the final follow-up date was May 26, 2019. We performed log-rank univariate analysis to compare patient demographic characteristics, biochemical tests and coagulation disturbances during the perioperative phase (the recorded coagulation function included examinations before the operation and on the first day after the operation). The significant factors for univariate analysis were analyzed by the Cox regression model. Kaplan-Meier (KM) plots were used to present the survival curves and analyze the crude survival between the two study groups (postoperative coagulopathy or not).

Furthermore, to explore which factors could lead to postoperative coagulation dysfunction, we first performed univariate and multivariate logistic regression analysis of the patient demographic characteristics, biochemical tests and perioperative factors. Univariate analysis was performed using Fisher’s exact test or the chi-square test to compare categorical variables. A P value < 0.05 was regarded as significant. Statistical analysis was carried out using IBM SPSS Statistics 20.0 (IBM, New York, NY).

Results

1 Postoperative coagulopathy in TBI patients is an important and independent factor affecting long-term survival

1.1 Patient survival

By May 26, 2019, 120 (26.8%) patients had died, 214 (47.9%) had survived, and 113 (25.3%) had been lost to follow-up. The follow-up duration was 1–53 months, and the
median time was 30 months. The survival analysis showed that the 1-year survival rate was 0.690 and that the 3-year survival rate was 0.607 (Fig. 1).

1.2 Log-rank univariate analysis of TBI patient prognosis

First, TBI patient prognosis with follow-up (334 cases) was compared with log-rank univariate analysis. Table 1 summarizes the variables upon admission and perioperative coagulation. According to the log-rank univariate analysis, the following factors were considered to be significantly associated with the survival of patients suffering from TBI: age (45-60 y, P = 0.015; >60 y, P < 0.001), AIS \textsubscript{(head)} = 5 (P < 0.001), GCS ≤ 8 (P < 0.001), abnormal pupil reaction (P < 0.001), systolic pressure at admission < 90 mmHg (P = 0.004), GLU > 151 mg/dL (P = 0.003), AST ≥ 40U/L (P = 0.049), K⁺ <3.5 mmol/L or > 5.5 mmol/L (P = 0.048), and postoperative coagulopathy (P = 0.007). The number of TBI patients < 45, 45–60, and > 60 was 87 (26.0%), 154 (46.1%), 93 (27.9%), respectively. In the group of patients < 45 years old, 17 (19.5%) died, while 70 (80.1%) survived. In the group of patients aged 45–60 years, 53 (34.4%) died, while 101 (65.6%) survived. In the group of patients > 60 years old, 50 (53.8%) died, while 43 (46.2%) survived. In terms of the severity of traumatic brain injury patients, which was based on the GCS score and AIS \textsubscript{(head)}, the number of GCS ≤ 8 were 97 (80.3%) in died group and 93 (43.5%) in survival group, respectively, while the number of AIS \textsubscript{(head)} = 5 were 83 (69.2%) in the death group and 64 (30.0%) in the survival group. A total of 112 (93.3%) TBI patients had abnormal pupil reactions in the death group, and 153 (71.5%) TBI patients had abnormal pupil reactions in the survival group. Ten patients had a systolic pressure < 90 mmHg at admission, and seven of these 10 patients died. In the death group, 91 (75.8%), 90 (75.0%) and 77 (64.2%) patients had abnormal glucose, ALT and K⁺ levels, respectively, in contrast to 124 (57.9%), 117 (54.7%) and 114 (53.3%) patients who had abnormal
glucose, ALT and K⁺ levels in the survival group. Interestingly, compared to preoperative coagulopathy, postoperative coagulopathy occurred in 75 of these 120 patients who died and 100 of these 214 patients who survived. However, there was no statistically significant difference in gender, midline shift, subarachnoid hemorrhage, multiple injury, GB, AST, BUN, Na⁺, Cl⁻, Ca²⁺, RBC, or preoperative coagulopathy between the death and survival groups, as shown in Table 1.

1.3 Cox regression model analysis for the influencing factors for TBI patient prognosis

Next, variables that were statistically significant according to the univariate analysis were analyzed using a Cox regression model. Multivariate Cox regression analysis identified age, AISₕ(ₜₜead) = 5, GCS ≤ 8, admission systolic pressure < 90 mmHg and postoperative coagulopathy as independent risk factors for survival following TBI (Table 2).

Interestingly, the postoperative coagulopathy was an independent risk factor, as we theoretically inferred. The 1-year survival rate of TBI patients suffering from postoperative coagulopathy was 0.625, and the 3-year survival rate was 0.558. Accordingly, the 1-year survival rate of TBI patients without postoperative coagulation dysfunction was 0.762 and the 3-year survival rate was 0.683. (Fig. 2)

2 Risk factors for postoperative coagulopathy in TBI patients

2.1 Patient Demographics

In this section, we explored which factors contributed to postoperative coagulopathy. In total, 447 patients were admitted for further analysis, and 215 patients had postoperative coagulopathy. Table 3 lists the differences in variables at admission between patients with postoperative coagulopathy and those without postoperative coagulopathy. The severity of traumatic brain injury in patients based on AISₕ(ₜₜead) and GCS scores was statistically significant. The number of patients with AISₕ(ₜₜead) = 5 was 198 TBI patients, and
postoperative coagulopathy occurred in 115 of these 198 patients. The number of patients with a GCS score ≤ 8 was 248 TBI patients, and postoperative coagulopathy appeared in 145 of these 248 TBI patients. A total of 196 (84.5%) patients had abnormal pupil reactions in non-postoperative coagulopathy group, while 163 (75.8%) cases in postoperative coagulopathy group. The presence of multiple injury was also statistically significant (P = 0.006). Postoperative coagulopathy occurred in 98 (60.5%) of these 162 patients with multiple injury. Patient biochemical tests upon admission, including hemoglobin (P = 0.001), ALT (P = 0.001), AST (P < 0.001) and RBC (P < 0.001) were also statistically significant. Other variables were not statistically significant, as shown in Table 3.

2.2 Perioperative Characteristics

The differences in perioperative variables between the postoperative coagulopathy and non-postoperative coagulopathy groups are shown in Table 4. Eighty-four TBI patients were diagnosed with coagulopathy preoperatively, of whom 65 (77.4%) had postoperative coagulopathy. Only moderate and severe shock were statistically significant (P = 0.038). Crystalloid solution > 2900 mL or Colloidal solution > 1100 mL was statistically significant (P = 0.014, P < 0.001, respectively). The infusion of crystalloid and colloidal solutions, which amounted to more than 3450 mL, was a risk factor (P < 0.001), with a total of 167 patients. A total of 108 (64.7%) of these 167 patients had postoperative coagulopathy. Similarly, net-fluid-input > 2425 mL was statistically significant (P = 0.001). In the non-postoperative coagulopathy group, intraoperative bleeding exceeded 950 mL in 87 (40.5%) patients, and in 154 (66.4%) patients in the postoperative coagulopathy group (P < 0.001). A total of 306 TBI patients received decompressive craniectomy, 175 of these 306 cases had postoperative coagulopathy (P < 0.001). The total surgery time, which was more than 3.225 hours, was statistically significant (P = 0.017).
2.3 Multivariate logistic regression analysis of postoperative coagulopathy in TBI patients

Next, we used a forward stepwise binary logistic regression model to examine the statistically significant factors in the univariate analysis. The statistically significant factors after logistic regression are shown in Table 5. Multivariate analysis identified abnormal ALT (P = 0.003) and RBC (P < 0.001) at admission, preoperative coagulopathy (P < 0.001), infusion of colloidal solution more than 1100 mL (P < 0.001), and intraoperative bleeding > 950 mL (P < 0.001) as independent risk factors for postoperative coagulation following TBI (Table 5).

Discussion

This study is the first analysis of the relationship between TBI patient outcomes requiring surgery and coagulopathy during the perioperative period performed using a survival analysis, and it analyzed the potential risk factors causing perioperative coagulopathy for the first time. We found that postoperative coagulopathy was identified as an independent risk factor for survival following TBI. The risk factors that contributed to postoperative coagulopathy included abnormal ALT and RBC at admission, preoperative coagulopathy, infusion of colloidal solution > 1100 mL and intraoperative bleeding > 950 mL.

Approximately 334 TBI patients underwent surgery and completed follow-up, with a 1-year survival rate of 0.690 and a 3-year survival rate of 0.607. Interestingly, we found that the 1-year survival rate decreased rapidly to 0.690, while the 3-year survival rate decreased by only 0.083 (Fig. 1). This suggests that TBI patient deaths in those who underwent surgery were concentrated in the first year. In other words, if the patient made it through the first year, his or her chances of survival were high.

In the log-rank univariate analysis, we found that age, AIS (head) = 5, GCS ≤ 8, abnormal pupil reaction, systolic pressure < 90 mmHg at admission, abnormal glucose, AST and K+
were statistically significant. In the Cox regression model analysis, age, AIS_{(head)} = 5, GCS \leq 8, systolic pressure at admission < 90 mmHg and postoperative coagulopathy were identified as independent risk factors. Age, whether 45–60 years or > 60 years, was statistically significant. Older age was analyzed as a significant predictor of prognosis in TBI [25, 26], which was also showed in our study. Moreover, we found that TBI was most common in patients aged 45–60 years old, which amounted to 154 (46.1%) patients, and the older the age group was, the more significant the difference was. Undoubtedly, the GCS score and AIS_{(head)}, which describe the severity of traumatic brain injury patients, are crucial factors affecting long-term survival, as previous literature has proved [26]. There were only 10 TBI patients whose systolic pressure at admission was < 90 mmHg because prehospital infusion was performed to stabilize blood pressure. Postoperative coagulation dysfunction is an independent risk factor for long-term survival, which is worth further attention. We would like to add that we did not include coagulation dysfunction at admission because of the particularity of patients with traumatic brain trauma undergoing surgery. Most of these patients requiring surgery were operated on within a few hours of admission. Preoperative coagulation function will overlap to some extent. In light of this, it is reasonable in a sense that we did not include coagulation function at admission.

The 1-year and 3-year survival rates of TBI patients suffering from postoperative coagulopathy were 0.625 and 0.558, respectively, which were accordingly below the overall survival rate. In contrast, the 1-year and 3-year survival rates of TBI patients with normal coagulation were 0.762 and 0.683, respectively, which were accordingly above the overall survival rate (Fig. 2).

Preoperative coagulopathy was an independent risk factor for postoperative coagulation disorders. This suggests that if there is enough time, we should actively design the plan for preventing the possible postoperative coagulation disorders before surgery; otherwise,
we should pay close attention to the factors which may have impact on coagulation condition during and after the operation. The infusion of crystalloid solution > 2900 mL, colloidal solution > 1100 mL or their sum > 3450 mL, and the net-fluid-input > 2425 mL were all statistically significant. On the one hand, the infusion of large amounts of fluid results in the dilution of coagulation factors in the plasma. On the other hand, whether the input of a large amount of fluid during surgery will cause the further release of brain-derived molecules to the circulatory system of the whole body and further aggravate coagulation disorders remains a question that deserves additional attention and research, because of the basic experimental evidence that pro-coagulant molecules (such as tissue factors, phosphatidylserine, cardiolipin, and vWF) are released from damaged brain tissue [27–29]. In this study, there was no definite ratio between crystal infusion and colloid infusion, and there was no significant difference between the two groups (data not shown).

Interestingly, intraoperative infusion of colloidal solution > 1100 mL was identified as an independent risk factor in the multivariate logistic regression analysis. Previous studies have shown that large amounts of colloid infusion can affect the body coagulation function [30, 31], which was also confirmed in this study. Furthermore, we found that when the intraoperative input of colloidal fluid was more than 1100 mL, the impact on postoperative coagulation was significant. This threshold is derived from the ROC curve (Supplementary Fig. 2). However, this conclusion was drawn from our retrospective study. Therefore, it is necessary to carry out prospective clinical trials to study the infusion of colloids in patients with craniocerebral trauma.

There are currently no clear guidelines for fluid management during craniocerebral trauma surgery, although there are some other guidelines for surgical fluid management [30, 32, 33]. How to maintain the balance between wet and dry conditions is a question we all
need to consider, especially in traumatic brain injury, because we do not know whether the high perfusion of fluid during surgery will cause secondary damage to the brain or not. Just as our research provides evidence for the management of fluids during surgery, more evidence-based prospective experiments are needed to explore this issue. We need a model or algorithm to calculate the most appropriate fluid intake for patients with craniocerebral trauma that can not only maintain cerebral and systemic perfusion, but also avoid secondary injury to the brain caused by elevated cranial pressure owing to high perfusion. This appropriate fluid intake will maximize the benefit of patients.

There were several limitations in our study. First, this was a retrospective single-center article. Retrospective articles are not a substitute for prospective randomized controlled trials. There may be other data that we have not recorded that will affect our analysis. Second, owing to the long follow-up time, approximately 25.3% of patients were lost to follow-up. However, the loss to follow-up rate might be acceptable, compared to other studies [34].

Conclusion

Those who suffered from postoperative coagulopathy due to TBI had a higher risk for poor prognosis than those who did not. Closer attention should be paid to postoperative coagulopathy, and more emphasis should be placed on managing the underlying risk factors it. If there is enough time, we need to actively improve the patient's red blood cell and coagulation functions between admission and the beginning of surgery. We should try to control the total amount of intraoperative infusion, especially the amount of colloidal fluid, which should not exceed 1100 ml. At the same time, abnormal ALT and intraoperative bleeding >950 mL may also indicate the possibility of poor postoperative coagulation function.
Abbreviations

AIS: Abbreviated Injury Scale; GCS: Glasgow Coma Scale; FFP: Fresh Frozen Plasma; RBC: Red Blood Cell; GLU: Glucose; GB: Hemoglobin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; BUN: Blood Urea Nitrogen

Declarations

Acknowledgements

We thank AJE (www.age.com) for English language editing.

Authors’ contributions

QY and GS conceived the study and drafted the manuscript. CW collected the data and drafted the manuscript. SY and FD performed statistical analysis of the data. WX, LJ, ZG, WB, GH and LH read and revised the manuscript. All authors approved the final manuscript.

Funding

None

Availability of data and materials

All relevant data are shown in the published manuscript.

Competing interests

No conflict of interests

Ethics approval and consent to participate

This retrospective study was approved by Institutional Review Board, Tang Du Hospital, Fourth Military Medical University (Assigned No. 201909-13) and the requirement for informed consent was waived

Consent for publication

Yes
References

1. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545-602.

2. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil. 2006;21(5):375-8.

3. Dadhwal US, Pathak N. Damage Control Philosophy in Polytrauma. Med J Armed Forces India. 2010;66(4):347-9.

4. Mitra B, Tullio F, Cameron PA, Fitzgerald M. Trauma patients with the 'triad of death'. Emerg Med J. 2012;29(8):622-5.

5. Chen H, Xue LX, Guo Y, Chen SW, Wang G, Cao HL, et al. The influence of hemocoagulation disorders on the development of posttraumatic cerebral infarction and outcome in patients with moderate or severe head trauma. BioMed research international. 2013;2013:685174.

6. Laroche M, Kutcher ME, Huang MC, Cohen MJ, Manley GT. Coagulopathy after traumatic brain injury. Neurosurgery. 2012;70(6):1334-45.

7. Maegele M, Schochl H, Menovsky T, Marechal H, Marklund N, Buki A, et al. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management. Lancet Neurol. 2017;16(8):630-47.

8. Stein SC, Smith DH. Coagulopathy in traumatic brain injury. Neurocritical care. 2004;1(4):479-88.

9. Harhangi BS, Kompanje EJ, Leebeek FW, Maas Al. Coagulation disorders after traumatic brain injury. Acta neurochirurgica. 2008;150(2):165-75; discussion 75.

10. Zhang J, Jiang R, Liu L, Watkins T, Zhang F, Dong JF. Traumatic brain injury-
associated coagulopathy. Journal of neurotrauma. 2012;29(17):2597-605.

11. Chhabra G, Rangarajan K, Subramanian A, Agrawal D, Sharma S, Mukhopadhayay AK. Hypofibrinogenemia in isolated traumatic brain injury in Indian patients. Neurol India. 2010;58(5):756-7.

12. Greuters S, van den Berg A, Franschman G, Viersen VA, Beishuizen A, Peerdeman SM, et al. Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury. Critical care (London, England). 2011;15(1):R2.

13. Tang K, Kong X, Mao G, Qiu M, Zhu H, Zhou L, et al. Primary cerebral malignant melanoma: A case report with literature review. Medicine (Baltimore). 2017;96(4):e5805.

14. Sun Y, Wang J, Wu X, Xi C, Gai Y, Liu H, et al. Validating the incidence of coagulopathy and disseminated intravascular coagulation in patients with traumatic brain injury--analysis of 242 cases. British journal of neurosurgery. 2011;25(3):363-8.

15. Franschman G, Boer C, Andriessen TM, van der Naalt J, Horn J, Haitsma I, et al. Multicenter evaluation of the course of coagulopathy in patients with isolated traumatic brain injury: relation to CT characteristics and outcome. Journal of neurotrauma. 2012;29(1):128-36.

16. Talving P, Benfield R, Hadjizacharia P, Inaba K, Chan LS, Demetriades D. Coagulopathy in severe traumatic brain injury: a prospective study. The Journal of trauma. 2009;66(1):55-61; discussion -2.

17. Genet GF, Johansson PI, Meyer MA, Solbeck S, Sorensen AM, Larsen CF, et al. Trauma-induced coagulopathy: standard coagulation tests, biomarkers of coagulopathy, and endothelial damage in patients with traumatic brain injury. Journal of neurotrauma. 2013;30(4):301-6.

18. de Oliveira Manoel AL, Neto AC, Veigas PV, Rizoli S. Traumatic brain injury associated
coagulopathy. Neurocritical care. 2015;22(1):34-44.

19. Stein SC, Spettell C, Young G, Ross SE. Delayed and progressive brain injury in closed-head trauma: radiological demonstration. Neurosurgery. 1993;32(1):25-30; discussion -1.

20. Kumar MA, Cao W, Pham HP, Raju D, Nawalinski K, Maloney-Wilensky E, et al. Relative Deficiency of Plasma A Disintegrin and Metalloprotease with Thrombospondin Type 1 Repeats 13 Activity and Elevation of Human Neutrophil Peptides in Patients with Traumatic Brain Injury. Journal of neurotrauma. 2019;36(2):222-9.

21. Dekker SE, Duvekot A, de Vries HM, Geeraedts LM, Jr., Peerdeman SM, de Waard MC, et al. Relationship between tissue perfusion and coagulopathy in traumatic brain injury. J Surg Res. 2016;205(1):147-54.

22. Yuan Q, Yu J, Wu X, Sun YR, Li ZQ, Du ZY, et al. Prognostic value of coagulation tests for in-hospital mortality in patients with traumatic brain injury. Scand J Trauma Resusc Emerg Med. 2018;26(1):3.

23. Lustenberger T, Talving P, Kobayashi L, Barmparas G, Inaba K, Lam L, et al. Early coagulopathy after isolated severe traumatic brain injury: relationship with hypoperfusion challenged. The Journal of trauma. 2010;69(6):1410-4.

24. Alexiou GA, Lianos G, Fotakopoulos G, Michos E, Pachatouridis D, Voulgaris S. Admission glucose and coagulopathy occurrence in patients with traumatic brain injury. Brain Inj. 2014;28(4):438-41.

25. Flaada JT, Leibson CL, Mandrekar JN, Diehl N, Perkins PK, Brown AW, et al. Relative risk of mortality after traumatic brain injury: a population-based study of the role of age and injury severity. Journal of neurotrauma. 2007;24(3):435-45.

26. Baum J, Entezami P, Shah K, Medhkour A. Predictors of Outcomes in Traumatic Brain
27. Zhao Z, Wang M, Tian Y, Hilton T, Salsbery B, Zhou EZ, et al. Cardiolipin-mediated procoagulant activity of mitochondria contributes to traumatic brain injury-associated coagulopathy in mice. Blood. 2016;127(22):2763-72.

28. Wu Y, Liu W, Zhou Y, Hilton T, Zhao Z, Liu W, et al. von Willebrand factor enhances microvesicle-induced vascular leakage and coagulopathy in mice with traumatic brain injury. Blood. 2018;132(10):1075-84.

29. Tian Y, Salsbery B, Wang M, Yuan H, Yang J, Zhao Z, et al. Brain-derived microparticles induce systemic coagulation in a murine model of traumatic brain injury. Blood. 2015;125(13):2151-9.

30. Rasmussen KC. Effect of perioperative colloid and crystalloid fluid therapy on coagulation competence, haemorrhage and outcome. Dan Med J. 2016;63(9).

31. Muralidhar K, Garg R, Mohanty S, Banakal S. Influence of colloid infusion on coagulation during off-pump coronary artery bypass grafting. Indian J Anaesth. 2010;54(2):147-53.

32. Schramko A, Suojaranta-Ylinen R, Kuitunen A, Raivio P, Kukkonen S, Niemi T. Hydroxyethylstarch and gelatin solutions impair blood coagulation after cardiac surgery: a prospective randomized trial. Br J Anaesth. 2010;104(6):691-7.

33. Kozek-Langenecker SA. Fluids and coagulation. Curr Opin Crit Care. 2015;21(4):285-91.

34. Bouzat P, Ageron FX, Thomas M, Vallot C, Hautefeuille S, Schilte C, et al. Modeling the Influence of Age on Neurological Outcome and Quality of Life One Year after Traumatic Brain Injury: A Prospective Multi-Center Cohort Study. Journal of neurotrauma. 2019;36(17):2506-12.

Tables
|                | Died (n=120) | Survival (n=214) | \(\chi^2\) Value | P-value |
|----------------|--------------|------------------|-------------------|---------|
| **Age**        |              |                  |                   |         |
| < 45 years     | 17           | 70               |                   |         |
| 45-60 years    | 53           | 101              | 5.967             | 0.015*  |
| > 60 years     | 50           | 43               | 22.883            | <0.001**|
| **Gender**     |              |                  |                   |         |
| Female         | 26           | 54               |                   |         |
| Male           | 94           | 160              | 0.764             | 0.382   |
| **AIS (head)***|              |                  |                   |         |
| < 5            | 37           | 150              |                   |         |
| = 5            | 83           | 64               | 48.157            | <0.001**|
| **GCS**        |              |                  |                   |         |
| > 8            | 23           | 121              |                   |         |
| \(\leq\) 8    | 97           | 93               | 40.965            | <0.001**|
| **Pupil reaction** |          |                  |                   |         |
| Normal         | 8            | 61               |                   |         |
| Abnormal       | 112          | 153              | 18.147            | <0.001**|
| **Midline shift** |          |                  |                   |         |
| No             | 73           | 120              |                   |         |
| Yes            | 47           | 94               | 0.350             | 0.554   |
| **Subarachnoid hemorrhage** |      |                  |                   |         |
| No             | 38           | 57               |                   |         |
| Yes            | 82           | 157              | 0.515             | 0.473   |
| **Multiple injury** |        |                  |                   |         |
| No             | 74           | 140              |                   |         |
| Yes            | 46           | 74               | 1.306             | 0.253   |
| **Systolic pressure at admission** |          |                  |                   |         |
| \(\geq\) 90 mmHg | 113         | 211              |                   |         |
| < 90 mmHg      | 7            | 3                | 7.365             | 0.004** |
| **GLU**        |              |                  |                   |         |
| \(\leq\) 151 mg/dL | 29          | 90               |                   |         |
| > 151 mg/dL    | 91           | 124              | 8.576             | 0.003** |
| Test  | Normal Range (Units/L) | Abnormal Range (Units/L) | Count 1 | Count 2 | Mean | Standard Deviation |
|-------|------------------------|--------------------------|---------|---------|------|-------------------|
| GB    | ≥ 120 g/L              | < 120 g/L                | 94      | 168     |      |                   |
|       |                        |                          | 26      | 46      | 0.041| 0.839             |
| AST   | < 40 U/L               | ≥ 40 U/L                 | 30      | 77      |      |                   |
|       |                        |                          | 90      | 137     | 3.868| 0.049*            |
| ALT   | < 40 U/L               | ≥ 40 U/L                 | 58      | 97      |      |                   |
|       |                        |                          | 62      | 117     | 0.373| 0.542             |
| BUN   | ≤ 7.1×10^{12}/L        | > 7.1×10^{12}/L          | 107     | 192     |      |                   |
|       |                        |                          | 13      | 22      | 0.079| 0.779             |
| K     | Normal                 | Abnormal                 | 43      | 100     |      |                   |
|       |                        |                          | 77      | 114     | 3.927| 0.048*            |
| Na    | Normal                 | Abnormal                 | 72      | 137     |      |                   |
|       |                        |                          | 48      | 77      | 0.431| 0.511             |
| CI    | Normal                 | Abnormal                 | 74      | 123     |      |                   |
|       |                        |                          | 46      | 91      | 0.465| 0.495             |
| Ca    | Normal                 | Abnormal                 | 42      | 74      |      |                   |
|       |                        |                          | 78      | 140     | 0.001| 0.973             |
| RBC   | Normal                 | Abnormal                 | 93      | 177     |      |                   |
|       |                        |                          | 27      | 37      | 1.388| 0.239             |
| Preoperative coagulation | Normal                 | Abnormal                 | 92      | 178     |      |                   |
|       |                        |                          | 28      | 36      | 3.702| 0.054             |
| Postoperative coagulation | Normal                 | Abnormal                 | 45      | 114     |      |                   |
|       |                        |                          | 75      | 100     | 7.290| 0.007**           |

* P < 0.05, ** P < 0.01
Table 2 Independent factor between death and survival (Multivariate Cox regression)

| Age             | B     | SE    | Wald   | df | Sig.   | Exp(B) |
|-----------------|-------|-------|--------|----|--------|--------|
| < 45 years      | 0.8435| 0.2893| 8.5014 | 1  | 0.003**| 2.3246 |
| 45-60 years     | 1.2760| 0.2870| 19.7610| 1  | <0.001**| 3.5823 |
| > 60 years      | 0.8201| 0.2360| 12.0746| 1  | 0.001**| 2.2707 |
| AIS(head) = 5   | 0.7719| 0.2786| 7.6738 | 1  | 0.006**| 2.1638 |
| GCS ≤ 8         | 1.1709| 0.4116| 8.0909 | 1  | 0.004**| 3.2248 |
| Systolic pressure at admission < 90mmHg | 0.4145| 0.1938| 4.5745 | 1  | 0.032* | 1.5136 |

* P < 0.05, ** P < 0.01

Table 3 Variables at admission between postoperative coagulopathy and not postoperative coagulopathy (Univariate analysis)

| Age             | Not postoperative coagulopathy (n=215) | Postoperative coagulopathy (n=232) | χ2 -value | P-value |
|-----------------|----------------------------------------|------------------------------------|-----------|---------|
| < 45 years      | 57                                     | 60                                 | 0.360     | 0.548   |
| 45-60 years     | 107                                    | 98                                 | 0.533     | 0.216   |
| > 60 years      | 51                                     | 74                                 | 1.533     | 0.216   |
| Gender          |                                        |                                    |           |         |
| Female          | 52                                     | 46                                 |           |         |
| Male            | 163                                    | 186                                | 1.238     | 0.266   |
| AIS(head)       |                                        |                                    |           |         |
| < 5             | 132                                    | 117                                |           |         |
| = 5             | 83                                     | 115                                | 5.437     | 0.020*  |
| GCS             |                                        |                                    |           |         |
| > 8             | 112                                    | 87                                 |           |         |
|                                      | ≤ 8  | 145 | 9.621 | 0.002** |
|-------------------------------------|------|-----|-------|---------|
| Pupil reaction                      |      |     |       |         |
| Normal                              | 52   | 36  |       |         |
| Abnormal                            | 163  | 196 | 5.304 | 0.021*  |
| Midline shift                       |      |     |       |         |
| No                                  | 121  | 136 |       |         |
| Exist                               | 94   | 96  | 0.250 | 0.617   |
| Subarachnoid hemorrhage             |      |     |       |         |
| No                                  | 65   | 59  |       |         |
| Exist                               | 150  | 173 | 1.283 | 0.257   |
| Multiple injury                     |      |     |       |         |
| No                                  | 151  | 134 |       |         |
| Yes                                 | 64   | 98  | 7.514 | 0.006** |
| Admission systolic pressure         |      |     |       |         |
| ≥ 90 mmHg                           | 209  | 225 |       |         |
| < 90 mmHg                           | 6    | 7   | 0.020 | 0.887   |
| GLU                                 |      |     |       |         |
| ≤ 151 mg/dL                        | 139  | 155 |       |         |
| > 151 mg/dL                        | 76   | 77  | 0.351 | 0.553   |
| GB                                  |      |     |       |         |
| ≥ 120 g/L                           | 185  | 169 |       |         |
| < 120 g/L                           | 30   | 63  | 11.803| 0.001** |
| AST                                 |      |     |       |         |
| < 40U/L                             | 83   | 52  |       |         |
| ≥ 40U/L                             | 132  | 180 | 13.877| <0.001**|
| ALT                                 |      |     |       |         |
| < 40 U/L                            | 120  | 93  |       |         |
| ≥ 40 U/L                            | 95   | 139 | 11.066| 0.001** |
| BUN                                 |      |     |       |         |
| ≤ 7.1×10^{12}/L                     | 195  | 201 |       |         |
| > 7.1×10^{12}/L                     | 20   | 31  | 1.820 | 0.177   |
| Variable       | Not postoperative coagulopathy (n=215) | Postoperative coagulopathy (n=232) | $\chi^2$-value | P-value |
|----------------|---------------------------------------|-----------------------------------|----------------|---------|
| Preoperative coagulation |                                      |                                   |                |         |
| Normal         | 196                                   | 167                               |                |         |
| Abnormal       | 19                                    | 65                                | 26.900         | <0.001**|
| Preoperative systolic pressure |                                      |                                   |                |         |
| $\geq$ 90 mmHg | 211                                   | 224                               |                |         |
| $<$ 90 mmHg    | 4                                     | 8                                 | 1.077          | 0.299   |
| Preoperative shock index |                                      |                                   |                |         |
| Normal         | 43                                    | 41                                |                |         |
| Mild shock     | 149                                   | 147                               | 0.019          | 0.890   |

* P < 0.05, ** P < 0.01

Table 4 Perioperative variables between postoperative coagulopathy and not postoperative coagulopathy (Univariate analysis)
| Category                                      | ≤ 2900 mL | > 2900 mL | p-value | Conclusion  |
|----------------------------------------------|-----------|-----------|---------|-------------|
| Moderate or severe shock                     | 23        | 44        | 0.038*  |             |
| Crystalloid solution                         | 176       | 167       |         |             |
| ≤ 2900 mL                                   | 39        | 65        | 0.014*  |             |
| Colloidal solution                           | 193       | 173       |         |             |
| ≤ 1100 mL                                   | 22        | 59        | <0.001**|             |
| Infusion of Crystalloid + Colloidal solution | ≤ 3450 mL | 156       | 124     |             |
| ≥ 3450 mL                                   | 59        | 108       | <0.001**|             |
| The ratio of infusion Plasma to RBC          | ≤ 1       | 20        | 40      |             |
| ≥ 1                                         | 105       | 150       | 0.264   |             |
| Intraoperative bleeding                      | ≤ 950 mL  | 128       | 78      |             |
| > 950 mL                                    | 87        | 154       | <0.001**|             |
| Net-fluid-input                              | ≤ 2425 mL | 168       | 149     |             |
| > 2425 mL                                   | 47        | 83        | 0.001** |             |
| Received Decompressive Craniectomy           | No        | 80        | 57      |             |
| Yes                                         | 131       | 175       | <0.001**|             |
| Total surgery time                           | ≤ 3.225 h | 55        | 38      |             |
| > 3.225 h                                   | 160       | 194       | 0.017*  |             |

* P < 0.05, ** P < 0.01
Table 5 Independent factor between postoperative coagulopathy and not postoperative coagulopathy (multivariate logistic regression)

| Factor                              | B     | SE    | Wald  | df | Sig.     | Exp(B) | lower limit |
|-------------------------------------|-------|-------|-------|----|----------|--------|-------------|
| Abnormal ALT at admission           | 0.6208| 0.2111| 8.6458| 1  | 0.003**  | 1.8605 | 1.2300      |
| Abnormal RBC at admission           | 1.0907| 0.2777| 15.4298| 1  | <0.001** | 2.9764 | 1.7272      |
| Preoperative coagulopathy           | 1.2927| 0.3023| 18.2804| 1  | <0.001** | 3.6426 | 2.0140      |
| Intraoperative infusion of Colloidal solution > 1100 mL | 1.0797| 0.2975| 13.1602| 1  | <0.001** | 2.9428 | 1.6425      |
| Intraoperative bleeding > 950 mL    | 0.8254| 0.2139| 14.8931| 1  | <0.001** | 2.2829 | 1.5011      |

* P < 0.05, ** P < 0.01

Figures
Figure 1

Kaplan-Meier survival curves for TBI patients undergoing surgery.
Figure 1

Kaplan-Meier survival curves for TBI patients undergoing surgery.
Figure 2

Kaplan-Meier survival curves for TBI patients undergoing surgery according to the postoperative coagulation function group (p = 0.007, log-rank test).
Figure 2
Kaplan-Meier survival curves for TBI patients undergoing surgery according to the postoperative coagulation function group (p = 0.007, log-rank test).

Supplementary Files
This is a list of supplementary files associated with the primary manuscript. Click to download.
SI.zip
SI.zip