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Acquired Factor XIII Deficiency in Patients with Multiple Trauma

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ABSTRACT

Introduction: Fibrin stabilizing factor (FXIII) plays a crucial role in blood clotting, tissue repair, and immune defense. FXIII deficiency after trauma can lead to prolonged wound healing due to persistent infections or coagulation disorders.

The aim of this study was to describe the prevalence of acquired FXIII deficiency after trauma and to provide a description of the time-course changes of important coagulation parameters in relation to FXIII activity. In this context, patient characteristics, laboratory data, and treatment modalities were examined with respect to their influence on FXIII activity. Furthermore, the effects of in vitro administration of FXIII on clot firmness and outcomes in patients with severe traumatic brain injury were investigated.

Patients and Methods: Two trauma cohorts (A and B) were examined prospectively in a two-center study, and another (cohort C) was examined retrospectively. In cohort A (trauma patients, n=880) routine laboratory tests were conducted, and FXIII activity was measured. In cohort B (polytrauma patients, n=26), additional clinical parameters were collected, and in-vitro FXIII administration and rotational thromboelastometry (ROTEM) analyses were performed. In cohort C (polytrauma patients with severe traumatic brain injury [sTBI], n=84), the impact of initially measured FXIII activity on clinical outcomes after sTBI was investigated using the modified Rankin Scale (mRS) at least 6 months after trauma.

Results: The prevalence of FXIII activity <70% in cohort A was 12.4%, with significant differences in age, Hb, fibrinogen, and Hct levels, platelet count, aPTT, and INR (vs. prevalence of FXIII activity >70%). Cohort B showed a decrease in FXIII activity from 85% to 58% after 7 days. FXIII deficiency correlated with time after trauma, aPTT, and fibrinogen level, lactate, and Hb levels. In-vitro administration of FXIII showed a positive influence on clot firmness due to improved maximum clot firmness (MCF in FIBTEM) and reduced maximum lysis (ML in EXTEM). Finally, a significant difference in FXIII activity between patients after sTBI with good and poor clinical outcomes was observed 6 months after trauma.

Conclusion: We demonstrated that trauma-associated FXIII deficiency is a common coagulation disorder, with FXIII deficiency increasing further in the first 7 days after trauma, the period of early surgical care. In vitro administration of FXIII was able to demonstrate significant clot stabilizing effects. For trauma

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patients with sTBI, FXIII activity could serve as a prognostic parameter, as it differed significantly between patients with good and poor clinical outcomes.

Introduction

Worldwide, 10% of deaths result from trauma. Approximately half of these trauma cases die from hemorrhage [1–3]. Severe cases carry the risk of developing complications associated with bleeding, such as trauma-induced coagulopathy (TIC) [2], which reflects the severity of the injuries and correlates with increased overall mortality [4,5]. Upon admission, 25-35% of trauma patients are coagulopathic [6] due to dilution, loss and consumption of coagulation factors [3,4]. Additionally, the early activation of protein C results in systemic anticoagulation and hyperfibrinolysis. Other aggravating factors, including acidosis, anemia, and electrolyte shifts, also occur [1,3,4,6].

The exact nature of (fibrin-stabilizing factor) FXIII deficiency in trauma patients remains unclear. Decreased FXIII activity may occur congenitally or may stem from increased turnover, consumption (trauma, bacteremia, thrombosis), or decreased synthesis levels caused by liver diseases [7–9].

FXIII has a significant effect on clot stability and wound healing [7,10]. Therefore, lower levels of FXIII may be associated with an increased risk of bleeding [11]. Moreover, administration of high-dose FXIII has been shown to be effective for hemostasis in in vitro trauma-associated coagulopathy and in vivo in model-induced hemorrhagic shock in rats [2]. The role of FXIII after trauma remains poorly investigated, especially the necessary activity level required to maintain adequate hemostasis [12]. Some case reports have shown disturbed wound healing in through protracted bloody-putrid wound secretion without evidence of a bleeding source, as well as absent signs of wound healing in surgical patients with FXIII activity <60%. Our clinical experience suggests that the administration of FXIII at low plasma levels may reduce the occurrence of postoperative complications, such as delayed wound healing [13–15].

However, the evidence to define the predictive factors triggering critical FXIII deficiency is lacking [3]. Moreover, clinical evidence suggests that over-consumption (severe trauma, disseminated intravascular coagulation, surgical procedures, sepsis, thromboembolic events) or inadequate synthesis (liver disease, leukemia, various medications) may predispose patients to acquired FXIII deficiency [16]. Furthermore, no uniform cutoff value exists to define FXIII deficiency.

Therefore, the aim of this study was to investigate the prevalence of FXIII deficiency in trauma patients, describe the temporal trend of certain coagulation parameters and FXIII activity after trauma, describe the effects of in-vitro administration of FXIII on clot firmness using thromboelastometry and investigate the association between FXIII activity and clinical parameters in acquired FXIII deficiency. In addition, the clinical outcomes of patients after severe traumatic brain injury in relation to FXIII activity on admission are described.

The execution was approved by the responsible ethics committee (ethical vote EA 2/51/11; EK 256072013).

Patients and Methods

This two-center study included three separate cohorts.

Cohort A (Dresden, n=880, 2016–2018) included polytrauma patients (classified according to the S3-guideline for multiple trauma [17]) who were admitted to the resuscitation room at University Hospital Dresden, Germany between January 1, 2016, to December 31, 2018. Upon admission, routine laboratory tests were conducted, and FXIII activity was measured. FXIII was quantified using the factor XIII-K assay (Kamiya Biomedical Company, Seattle, WA, USA) on a STAR Max3 coagulation system (STAGO GmbH, Düsseldorf, Germany). The assay utilizes an FXIII-specific antibody and an immunological turbidimetric method. Quantification was based on a multipoint calibration curve. These prospectively collected data were analyzed descriptively to determine the prevalence of acquired FXIII deficiency (for our considerations defined as FXIII activity <70%) in severely injured patients and to characterize other clinical and laboratory (Hb, Hct, and fibrinogen levels, platelet count, aPTT, International Normalized Ratio [INR], leukocyte count, D-dimers) parameters in patients with FXIII activity <70%. Congenital FXIII deficiency was an exclusion criterion. Data sets were divided into two groups (FXIII > 70% and FXIII ≤ 70%) and compared by Mann-Whitney test. No follow-up was performed during descriptive cross-sectional data collection. Inclusion was independent of injury pattern, and the taking of coagulation-related medication. However, the aim was to include a representative patient spectrum without selection bias.

Cohort B (Berlin, n=26, 2011–2014) included severely injured polytrauma patients recruited at Charité - University Medicine Berlin, Germany, between January 1, 2011, to December 31, 2014. Inclusion criteria were age ≥18 years, Injury Severity Score (ISS) ≥15, and admission within 2 hours or transferred within 6 hours after trauma. Patients with severe traumatic brain injury (Glasgow Coma Scale (GCS) ≤ 9 on scene, Abbreviated Injury Score (AIS) head ≥ 4), pregnancy, and known coagulation disorders were excluded. Laboratory tests (including FXIII activity) were conducted upon admission (baseline), and at 6, 24, 48, 72, and 168 h after hospital admission. The influence of in-vitro FXIII administration on clot stability was investigated via rotational thromboelastometry (ROTEM) at given time points. Therefore, 16.30 µL of 0.9% saline (normal saline; NS), 1.5 IU FXIII (positive control 150%, p150), or 3 IU FXIII (positive control 300%, p300) was pipetted into a 650 µl citrate blood specimen from patients from cohort B. The dosage was calculated using common standards and FXIII concentrations. The normal value is assumed to be 14-28 mg FXIII/L or 0.7-1.4 IU/mL (70-140%). The aim of the in vitro experiment was to restore normal (150%) and supernormal FXIII activity (300%). Therefore, a normal value of 1 IU/mL (100%) was assumed, and equivalent doses of 1.5 IU/mL (150% of normal activity) and 3 IU/mL (300% of normal activity) were added. After incubation at room temperature for 20 min and homogenization, ROTEM was performed (2 channels EXTEM, FIBTEM: running time 2 hours). A deficiency of FXIII was defined in our study as an activity of ≤ 70%. Data were compared and described using two way ANOVA with Tukey post-hoc test.

Additionally, for each separate patient with at least 4 observations over the survey period, correlation coefficients were calculated between FXIII activity and patient characteristics (age, BMI, ISS, SOFA score), blood values (platelet count, INR, aPTT, pH, base excess, and lactate, hemoglobin, calcium, and fibrinogen levels), and time after trauma. The distributions of these correlations were examined and trends towards systematically positive or negative correlations were evaluated using the Wilcoxon Signed Rank Sum test (association was assumed if $p < 0.05$).

Table 1
Description of trauma patients with FXIII deficiency included in cohort A. Of the 880 included the 834 cases that had documented FXIII activity were considered. Median (IQR), Mann-Whitney test.

Parameter	FXIII ≤ 70% (n=103)	FXIII >70% (n=731)	p	$n_{\leq 70\%}$ vs $n_{>70\%}$
Age (years)	59 (35-75)	49 (31-64)	0.003	103 vs 731
Hb level (mmol/L)	6.8 (5.5-8.2)	8.5 (7.7-9.1)	< 0.001	101 vs 723
Hct level	0.3 (5.5-8.2)	0.4 (0.37-0.43)	< 0.001	101 vs 723
Platelet count (/µl)	173 (124-236)	221 (184-261)	< 0.001	100 vs 723
aPTT (s)	30 (26-37)	27 (25-29)	< 0.001	103 vs 731
INR	1.3 (1.2-1.6)	1.06 (1-1.14)	< 0.001	99 vs 731
Fibrinogen level (g/L)	1.9 (1.5-3)	2.8 (2.3-3.3)	< 0.001	103 vs 731
Leukocytes (10^3/µL)	11.6 (8.1-17.3)	10.8 (8-14.5)	0.106	101 vs 723

Confounding factors were the different injury patterns, the administration of blood products during the observation period, and the occurrence of complication courses and revision interventions, which was also accompanied by partially incomplete documentation of the variables under consideration.

Cohort C (Dresden, n=84, 2008-2013) included patients admitted after polytrauma and with severe traumatic brain injury (sTBI) to the emergency department of University Hospital Dresden, Germany, between March 1, 2008, and May 31, 2013. Inclusion criteria were age ≥ 15 years, ISS≥ 16, and sTBI with cerebral contusion or subdural hematoma (AIS head ≥ 3). Exclusion criteria were prior treatment with anticoagulants or antiplatelet agents and delayed transfer from external clinics. Data collection regarding Cohort C was part of the dissertation of one of the authors [18].

FXIII activity was determined prospectively at two time points ($FXIII_1$ and $FXIII_2$; the interval between measurements was 0.7 to 43.5 hours, interquartile range (IQR), 2.2-5 hours) and its association with follow-up outcome was investigated using the modified Rankin Scale (mRS_{FU}), at least 6 months after trauma (median of 37 months, interval 6 to 67). Similar to cohort B, the heterogeneous patient spectrum, the different injury patterns, and the different therapies were potential confounders.

In cohort A, only the cases with a complete data set were analyzed. In cohort B, isolated measurements of the prospective observation were not available. Statistical considerations were performed with the available data without excluding patients. The data set of included patents in cohort C was complete regarding the considered parameters.

GraphPad Prism version 9.0.1 for Mac (GraphPad Software Inc., San Diego, CA, USA) and SPSS (release 23 for Windows, IBM, Armonk, NY, USA) were used to calculate and visualize the results.

Results

Cohort A (Dresden, n=880, 2016-2018)

Prevalence and collective description of FXIII deficiency in trauma

The median age was 51 years (IQR, 31-66 years), and 70% of the patients were men. FXIII activity ≤ 70% occurred in 12.4% (n = 103) of patients. There were significant differences in age, Hb, Hct level, platelet counts, aPTT, INR, and fibrinogen level between the comparison groups. The detailed values are shown in Table 1. There was no significant difference between the leukocyte counts. In the 880 cases included, FXIII activity was determined and documented in 834 patients. The remaining 46 cases were excluded. D-dimers were recorded in the FXIII deficiency group in only 33 cases and were therefore excluded from consideration.

Cohort B (Berlin, n=26, 2011-2014)

The median age of the patients was 33 years (range, 21-79 years; IQR, 25-51 years), and 23% of the patients were women. The mean ISS was 30 (interval, 6-66; SD, 14). According to each organ system, the mean (range) AIS scores were 2 (0-5) for head, 1 (0-2) for neck, 3 (1-5) for thorax, 2 (1-5) for abdomen, and 3 (1-5) for extremities. 46% (n=12) of the patients developed SIRS, 19% (n=5) developed sepsis, 35% (n=9) had multiple-organ failure (MOF) during hospitalization, and 35% (n=9) underwent mass transfusion. 81% (n=21) of the patients received between 2 and 137 RBCs (mean 17 per patient), 65% (n=17) of the patients received between 2 and 137 FFPs (mean 28 per patient), 42% (n=11) of the patients received between 1 and 19 platelet concentrates (mean 5 per patient) during follow-up. The survival rate was 88.5% (n=23). One patient died on the day of admission, another on the 4th day of follow-up. Due to various reasons such as medical interventions, transfers or death, the time-dependent measurement series from cohort B are incomplete. The calculations concerning cohort B were nevertheless performed with the available data.

Kinetics of FXIII activity and selected coagulation parameters after severe multiple trauma

Concerning the monitored coagulation parameters and FXIII activity, the opposite tendency was observed over time (Fig. 1). Initially, the median (IQR) FXIII activity was 87% (61-98%). After 7 days, FXIII activity decreased to a median of 58% (52-71%). The INR displayed the same decreasing trend, initially starting at 1.4 (1.2-1.6) and decreasing to 1.2 (1.1-1.3) during the observation period. The initial median fibrinogen concentration of 2 g/L (1.5-2.5 g/L) and aPTT of 33.2 s (29.5-38.6 s) increased in values at 5.8 g/L (5.1-6.7 g/L) and at 37.6 s (34.7-41.5 s) by day 7, respectively.

Within patient correlation of FXIII deficiency with clinical parameters

FXIII deficiency showed a within patient correlation with time after trauma, aPTT, and fibrinogen, lactate, and Hb levels (table 2). However, no statistical correlation was shown between FXIII deficiency and SOFA score, platelet count, pH, base excess or calcium. According to the correlation directions, FXIII activity decreases with time after trauma, PTT increases with falling FXIII activity, lactate increases with FXIII activity, Hb level increases with FXIII activity. For age, BMI, and ISS, these correlations are not applicable because these parameters do not vary with time, but the FXIII values differ.

Thromboelastometry and in-vitro FXIII administration

A dose-dependent MCF and ML (in % clot lost, relative to MCF) by in-vitro administration of FXIII was observed using ROTEM. While MCF in the fibrin-based extrinsically activated test (FIBTEM) increased over time, the firmness was superior at all time points in the p150 group, but even more in the p300 group, in comparison to that in the NS group (SD). With 10.9 mm (6.39 mm; NS group), 12.8 mm (7.66 mm; p150 group), and 18.8 mm (14.9 mm; p300 group) on admission, MCF increased to 30.9 mm (10.7 mm; NaCL group), 40.5 mm (11.5 mm; p150 group), and 47.2 mm (14.4 mm; p300 group) by day 7 in the FIBTEM measurements. The control, p150 and p300 groups revealed significant differences in MCF from 24 hours to day 7 in the FIBTEM measurements (Fig. 2).

The ML in the tissue factor-based extrinsically activated test (EXTEM) of the p300 group also showed lower values than those of the p150 and NS groups after 6 hours (Fig. 3).

Upon admission, the p300 group showed a lower mean (SD) ML than the p150 group at 12% (21%) versus 14% (23%), which was higher than that in the control group with 14% (20%). After 6 hours and up to day 7, the values of the p300 group were lower than those in the p150 and control groups (Fig. 3: day 7: p300 group 5 [3%]; p150 group 8 [6%]; control group 10 [5%]). Despite this trend, shown in Fig. 3, there were no significant differences for ML in EXTEM (two way ANOVA with Tukey post-hoc test, $p > 0.1$).

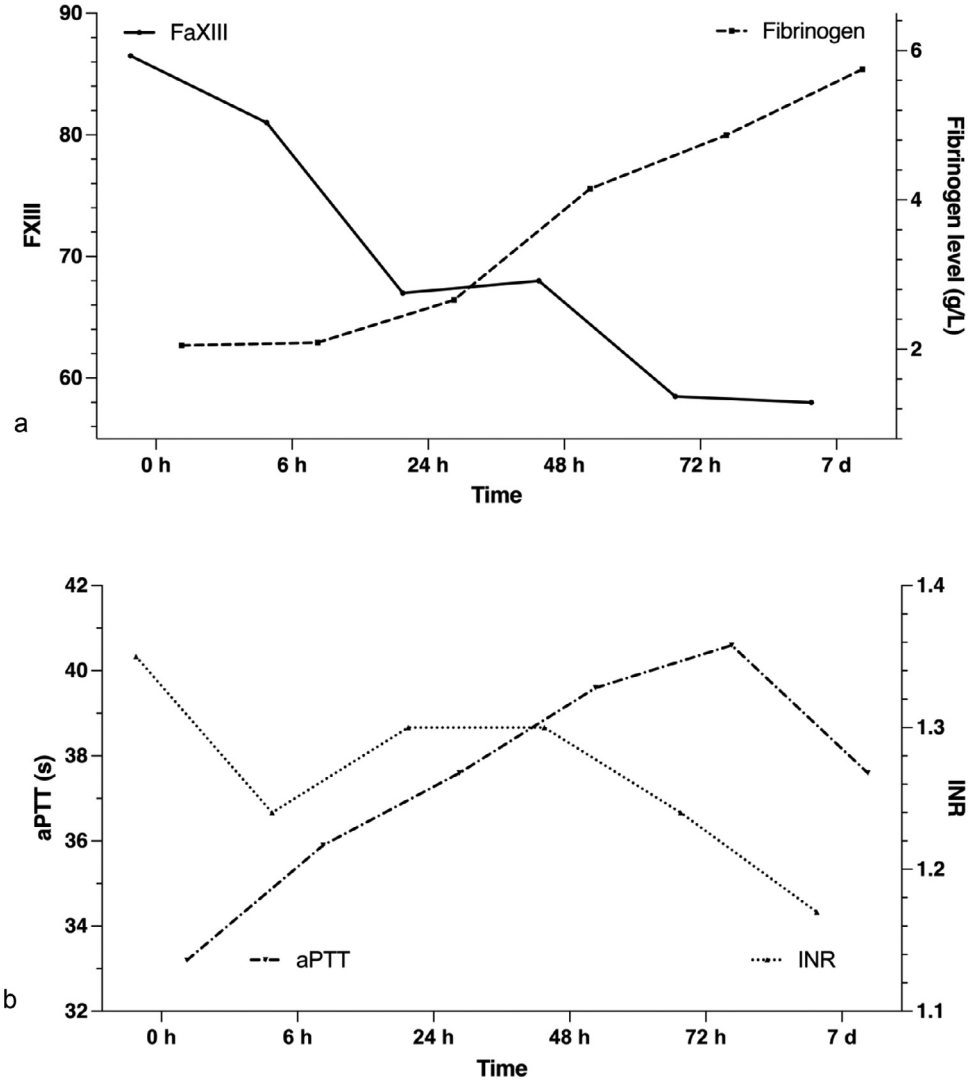

Fig. 1. Time-dependent opposing progression **a)** of FXIII activity (solid line), fibrinogen level (dashed line), and **b)** aPTT (dotted dashed line) and INR (dotted line) in multiple trauma (cohort B, medians at different time points, IQR not shown).

Table 2
Distributions of within patient correlations of FXIII values with other variables over different time points (Wilcoxon Signed Rank Sum test; *Number of patients with at least 4 observations).

	Median	Range		Quartile		IQR	n*	p-Value
		Min	Max	1st	3rd			
Time	-0,590	-0,944	0,596	-0,786	-0,306	0,480	21	**0,001**
SOFA	-0,164	-0,883	0,985	-0,558	0,056	0,614	12	0,347
INR	-0,167	-0,863	0,958	-0,602	0,094	0,696	21	0,079
aPTT	-0,734	-0,931	0,000	-0,795	-0,339	0,455	21	**<0.001**
Platelet Count	0,197	-0,745	0,722	-0,224	0,522	0,746	21	0,170
Fibrinogen	-0,580	-0,968	0,779	-0,744	-0,410	0,334	21	**0,001**
pH	-0,283	-0,961	0,702	-0,488	0,427	0,916	18	0,500
BE	0,046	-0,895	0,916	-0,619	0,604	1,223	16	0,918
Lactate	0,810	-0,513	0,996	0,473	0,902	0,428	17	**0,002**
Hb	0,591	-0,713	0,990	0,287	0,869	0,583	21	**0,004**
Calcium	0,044	-0,975	0,968	-0,156	0,431	0,588	17	0,554

Cohort C (Dresden, n = 84, 2008-2013)

Association of FXIII activity and clinical outcomes after polytrauma with severe traumatic brain injury

The median age of the injured patients was 41 years (range, 15-77 years; IQR, 28-59 years) and 75% (n = 63) of patients were men. The median FXIII activity was 87% at baseline ($FXIII_1$; interval, 33 to 177%; IQR, 69-108%) and decreased to 71% during the second measurement ($FXIII_2$; interval, 26 to 139%; IQR, 58-85%). At baseline and the second measurement, 17% of patients (n = 14) and 36% of patients (n = 30), respectively, displayed an FXIII activity <70%.

A significant difference in FXIII activity between good ($mRS_{FU} < 4$) and poor follow-up outcomes ($mRS_{FU} \geq 4$) was observed during

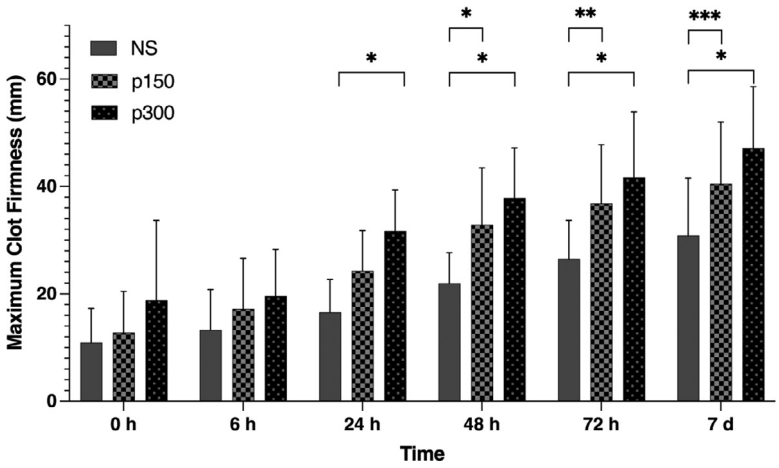

Fig. 2. Comparison of time-dependent progression of MCF in FIBTEM measurements among control (normal saline, NS), p150 (1.5 IU FXIII), and p300 (3 IU FXIII) group; significant differences between control p150 and p300 groups regarding MCF in the period of 24h – day 7 (cohort B, means with SD, two way ANOVA with Tukey post-hoc test, *p < 0.001, **p=0.003, ***p=0.024).

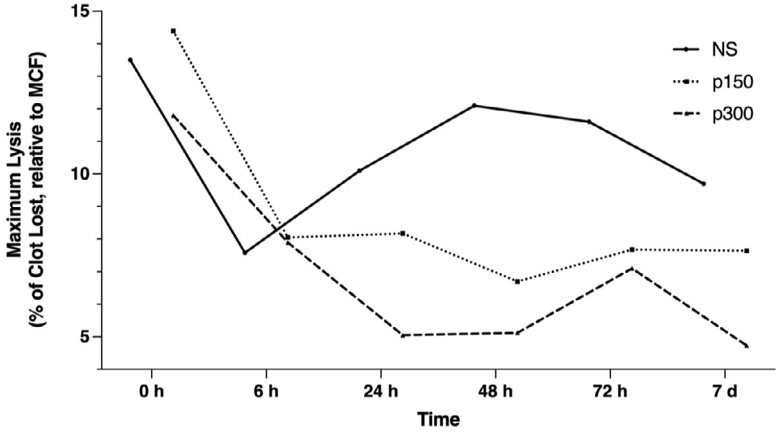

Fig. 3. Time-dependent progression of ML in EXTEM measurement among control (normal saline, NS), p150 (1.5 IU FXIII) and p300 (3 IU FXIII) groups (cohort B, means, cohort B, SD not shown).

the first and second measurements (Fig. 4). Thus, the median $FXIII_1$ activity was 73% (interval, 35-139%; IQR, 59-91%) for poor mid-term outcomes and 94% (interval, 42-177%; IQR, 76-113%) for good outcomes (Mann-Whitney test, *p = 0.002). The median $FaXIII_2$ activity was 60% (interval, 26 to 111%; IQR, 50-73%) for poor mid-term outcomes and 78% (interval, 49 to 139%; IQR, 65-139%) for good outcomes (Mann Whitney test, **p = 0.008).

Discussion

Trauma-induced coagulopathy is a common complication and remains a challenge for clinical management. TIC is described in 25-35% of patients after severe trauma [19–21]. In addition to hypoperfusion due to blood loss, serve trauma leads to tissue damage. In combination with acidosis and hypothermia, a generalized immune response with coagulation activation is induced, in which consumption of FXIII also plays an important role [22–24]. We detected an FXIII activity of <70% upon admission in 12.4% of patients in cohort A. Frith et al. described the dependence of the extent of coagulopathy on injury severity [19]. This was confirmed by our observation that 17% of more severely injured patients (cohort C) showed a deficiency in FXIII activity after sTBI.

The discrepancy between TIC and FXIII deficiency after trauma provides evidence of other causes of post-traumatic bleeding disorders [20,25]. Trauma-associated FXIII deficiency seems to occur less frequently than, factor V deficiency, which is found in up to 20% of patients [26], or fibrinogen deficiency, which is observed at early stages in the majority of severe trauma patients [27–32]. In cohort B (mean ISS of 30), a decreasing trend in FXIII activity was observed. It dropped to less than 70% between 6 and 24 hours after admission. aPTT showed an increasing trend during our observations. The increase in fibrinogen concentration could compensate for the deficiency of FXIII activity and hence explain the decreasing INR and rare clinical manifestation of FXIII deficiency, as regulatory effects of fibrinogen on FXIII have been described [33–35]. The opposing concentrations or activity trends of fibrinogen and FXIII, respectively, allow for multiple possible interpretations. The causes of FXIII deficiency have been previously described. The fibrinogen response may be due to its role as an acute-phase protein; its level also increases over time after surgical interventions [36,37]. Another reason may be the relative absence of thrombin. A key feature of the synchronization of coagulation processes is that thrombin converts fibrinogen into fibrin and initiates the process of activating FXIII. It is reasonable to assume that thrombin deficiency results in inadequate activation of FXIII and conversion of fibrinogen to fibrin [35].

In accordance with these findings, current guidelines still recommend using mass transfusion protocols in order to administer fresh frozen plasma, red blood cells, and platelets in a 4:4:1 ratio for cases of bleeding-related, life-threatening shock as coagulation therapy or if no point-of-care-testing is available [17,29,38–41]. FXIII deficiency should be considered as a coagulopathy that

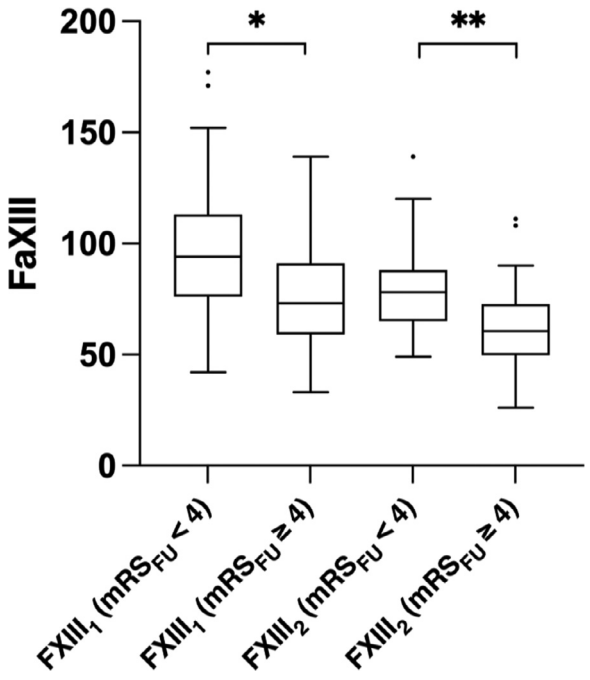

Fig. 4. Boxplot (median, Tukey-interval) of FXIII activity in Cohort C: at both time points, FXIII activity differed significantly between the good ($mRS_{FU} < 4$) and poor ($mRS_{FU} \geq 4$) mid-term outcome groups (Mann-Whitney test, $^{*}p = 0.002$; $^{**}p = 0.008$).

can lead to bleeding complications and consequently the administration of large amounts of blood products. This is confirmed by the current literature and by the correlations between Hb concentration and FXIII activity.

Three main influencing factors, the “first hit” (trauma), the “biological response”, and the “second hit” (surgery) substantially affect the clinical course of patients [21]. In this study, FXIII deficiency correlated with the time interval since trauma, aPTT, and fibrinogen, lactate, and Hb levels. The deranged coagulation status in the acute phase and decreasing FXIII activity in the subacute phase (within 7 days after trauma) of polytrauma patient management could correspond with the extensive definitive surgery on day 3-7 after trauma, leading to FXIII deficiency-associated complications (e.g. blood loss, wound healing problems, infection) [21,42,43]. In addition to the immunogenic stress caused by a “second hit” due to definitive surgical care, the coagulation situation can also deteriorate, and the risk of complications may increase [44,45]. To quantify the "first hit", parameters of the coagulation cascade, including FXIII activity, are reliable and recommended to be measured before planning definitive surgical care [21,43]. This is especially true when combined with other risk factors that imply hyperfibrinolysis and TIC (e.g., decreased fibrinogen level and FXIII activity) [46].

As demonstrated in rat models, the administration of high-dose FXIII has been shown to promote hemostasis in trauma-associated coagulopathy through improved clot strength and resistance to hyperfibrinolysis [47]. We were able to demonstrate a significant increase in MCF in FIBTEM measurements as well as a decrease in ML in EXTEM measurements after in-vitro administration of FXIII. Weight-adapted administration based on medical information refers to hereditary deficiency. Unfortunately, there is no uniform recommendation for acquired FXIII deficiency. However, clinical practice involves the administration of 1250 IU FXIII with subsequent activity monitoring in case of a deficiency [48]. The effect on MCF after in-vitro substitution increases over time, as FXIII deficiency seems to become more relevant in the post-acute phase after trauma according to the described declining kinetics. This also underlines the clinical relevance of a deficit when planning definitive surgical care or the deficit should be considered as a possible cause in complicative courses.

Aggravatingly, FXIII is known to play an important role not only in hemostasis but also in angiogenesis, wound healing, bone regeneration, and immune defense [49–51]. Previously, we described the effect of FXIII deficiency on wound healing and postoperative recovery in trauma patients [13–15]. In our experience, liver synthesis disorders, sepsis (especially due to staphylococci, streptococci, and enterococci), and large wound areas favor FXIII deficiency, which may lead to further complications. The coagulation status and subsequent risk of bleeding complications can be improved by the administration of FXIII after appropriate acute-phase diagnostics have been performed.

Our observations suggest a revision of mass transfusion protocols based on the European guideline for management of major bleeding and coagulopathy following trauma, which, to date, does not include a standardized administration of coagulation factors [48]. Furthermore, clinical studies on therapeutic applications are pending. Particularly in the first 24-144 hours after trauma, clot firmness may increase after FXIII administration (context of major surgery, damage control concept).

When measuring coagulation factors such as fibrinogen level and INR, there is a risk of misinterpretation because these showed conflicting courses in severe polytrauma patients (cohort B). Difficult to detect by classical coagulation diagnostics [52], FXIII deficiency can result in bleeding complications, even if hemostasis is initially intact [53]. Routine coagulation tests (INR, aPTT, Quick) may not indicate FXIII deficiency, and bleeding complications may negatively affect clinical outcomes. The observed correlation between FXIII activity and clinical outcomes (cohort C) may be explained by an increased occurrence of bleeding complications as a consequence of trauma-induced FXIII deficiencies caused by the release of tissue factor and an increased consumption of coagulation factors, which is described in particular after sTBI [46]. Similar observations have been described in surgical settings; decreased FXIII activity may be associated with an increased risk of postoperative bleeding after intracranial surgery [54,55].

A potential confounding factor could be the different injury patterns of a heterogeneous study population (cohort A, selected to determine prevalence in a representative collective without selection bias).

In addition, this study considers relatively small populations in cohorts B and C, owing to the severity of the injuries and the partial lack of completeness of the data. Nevertheless, cohort A represents a representative patient population. It can be assumed that the missing data in the observation period of cohort B influence the results. However, the observed trend is conclusive and needs to be corroborated by future studies with larger numbers of subjects. Another confounding factor is the administration of blood products, especially in Cohort B. It can be assumed that "native" blood values are different in the course than those after the (extensive) administration of blood products in the context of polytrauma management. However, as standardized treatment according to current guidelines it is therefore interesting to observe the described courses, especially under therapy with blood products. It should be assumed that deficiency effects are even more drastic without the administration of blood products.

Conclusion

The influence of FXIII deficiency on hemostasis, angiogenesis, wound healing, bone regeneration, and immune defense has been described previously.

In this study, we revealed a prevalence of 12.5-16.7% trauma associated FXIII deficiency at admission. Thus, we conclude that FXIII deficiency in trauma is quite common.

Furthermore, we were able to describe antidromic kinetics of FXIII activity as indicated by INR, aPTT, and fibrinogen level with median FXIII activity of 58% at 7 days after trauma. Decreased FXIII activity was associated with worse outcomes after sTBI. Additionally, we demonstrated the beneficial effects of FXIII administration on clot stability in our in-vitro experiment. All these effects, combined with our clinical experience, strongly indicate the importance of routine measurement of FXIII activity in trauma management, especially within the first week after trauma and before planned, extensive surgical reconstructions.

Further studies are needed to understand the full clinical relevance of FXIII activity and pathophysiologic pathways and to determine a safe cut-off value, especially between days 2 and 7 after trauma and prior to definitive surgical care ("second hit").

Declaration of Competing Interest

The Center for Musculoskeletal Surgery (CMSC) Charité - University Medicine Berlin, Germany was provided with TEG machines, TEG reagent and fibrogramin for in-vitro FXIII assays by CSL Behring Germany for the cohort B studies (cohort A/C no support). Christian Kleber has received honoraria from CSL Behring, Germany, which also supported the funding of the open access publication. The remaining authors have disclosed that they do not have any conflicts of interest.

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