



Mild Acquired Factor XIII Deficiency and Clinical Relevance at the ICU—A Retrospective Analysis

Clinical and Applied
Thrombosis/Hemostasis
Volume 27: 1-7
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DOI: 10.1177/10760296211024741
journals.sagepub.com/home/cat


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Abstract

Acquired FXIII deficiency is a relevant complication in the perioperative setting; however, we still have little evidence about the incidence and management of this rarely isolated coagulopathy. This study aims to help find the right value for the substitution of patients with an acquired mild FXIII deficiency. In this retrospective single-center cohort study, we enrolled critically ill patients with mild acquired FXIII deficiency (>5% and ≤70%) and compared clinical and laboratory parameters, as well as pro-coagulatory treatments. The results of the present analysis of 104 patients support the clinical relevance of FXIII activity out of the normal range. Patients with lower FXIII levels, beginning at <60%, had lower minimum and maximum hemoglobin values, corresponding to the finding that patients with a minimum FXIII activity of <50% needed significantly more packed red blood cells. FXIII activity correlated significantly with general coagulation markers such as prothrombin time, activated partial thromboplastin time, and fibrinogen. Nevertheless, comparing the groups with a cut-off of 50%, the amount of fresh frozen plasma, thrombocytes, PPSB, AT-III, and fibrinogen given did not differ. These results indicate that a mild FXIII deficiency occurring at any point of intensive care unit stay is also probably relevant for the total need of packed red blood cells, independent of pro-coagulatory management. In alignment with the ESAIC guidelines, the measurement of FXIII in critically ill patients with the risk of bleeding and early management, with the substitution of FXIII at levels <50%-60%, could be suggested.

Keywords

hemorrhage, factor XIII, critical care, blood transfusion, blood coagulation

Date received: 29 March 2021; revised: 11 May 2021; accepted: 24 May 2021.

Introduction

Factor XIII, also known as fibrin stabilizing factor, is the latest clotting factor to be discovered, influencing processes like wound healing and inflammation, among others.¹⁻⁴ Factor XIII is synthesized in the liver, platelets, and in macrophages/monocytes.⁵⁻⁷ A wide range of FXIII activity levels are described in the healthy population: from 53.2% to 221.3% and from 51% to 152% in 2 different studies.^{8,9} The effects on hemostasis are an enhanced clot stability, correlating with FXIII activity, and the crosslinking of alpha-2 plasmin inhibitor to fibrin, though early fibrinolysis is impaired.^{10,11} Congenital FXIII deficiency, partly with first symptoms at birth (e.g. prolonged or delayed umbilical bleeding and spontaneous cranial hemorrhage)^{8,12} and acquired FXIII deficiency, for example caused by major surgery, massive hemorrhage, sepsis, or acute liver failure are described.^{13,14} The delayed onset of these

bleeding episodes, from 12-36 hours, is pathognomonic of low FXIII activity.¹⁵ While congenital deficiency FXIII levels below 10% are described as a cut-off for substitution, a high-

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risk for spontaneous bleeding is defined at levels below 4%. It is still unclear which is the right cut-off value for patients with an acquired deficiency.^{8,13,16} Previous publications have already shown that decreased FXIII levels might be an indicator for re-exploration after cardio-thoracic surgery and anastomotic insufficiency.^{17,18} Therefore, FXIII activity levels of 50%-60% have been suggested in the past to prevent major perioperative complications.¹⁹⁻²²

In this context, it is important to classify the incidence and the need for treatment, especially for mild acquired FXIII deficiency, for a more evidence-based use of the different therapeutic options. In the past FXIII deficiency therapy consisted of the application of fresh frozen plasma (FFP) or cryoprecipitate. Today a plasma derived FXIII concentrate (Fibrogammin® P/Corifact™) and a recombinant FXIII product (containing only the A subunit) are available for targeted substitution of Factor XIII.^{23,24} In previous analyses regarding safety and efficacy, the use of the plasma derived product, as well as the application of recombinant FXIII, revealed a favorable safety profile.^{25,26}

In this retrospective single-center study, we enrolled patients with mild acquired FXIII deficiency (>5% and ≤70%) in an intensive care unit (ICU) and compared the clinical and laboratory parameters, as well as the pro-coagulatory treatments, of the different FXIII activity levels. The intention was to gain an idea of the level at which the acquired FXIII deficiency causes clinically relevant problems, and to find out if there are possible implications for the management of perioperative mild factor XIII deficiency.

Methods

The underlying study was planned as a retrospective cohort analysis. The study was conducted at 2 ICUs of the University Hospital Frankfurt. The period of recruitment was from October 2011 to July 2013. We screened for patients with mild Factor XIII deficiency in the ICU. The term “mild” was defined according to previous publications, as a FXIII activity under the normal range (<70%), but over 5%. In distinction to “moderate” (1%-4%) and “severe” (<1%) deficiency under normal conditions patients within this range do not show spontaneous bleeding or other specific symptoms of FXIII deficiency.^{27,28} The photometric determination of the activity of factor XIII in plasma samples was carried out with Berichrom® FXIII from Siemens (Marburg, Germany). In most cases, FXIII was analyzed routinely once a week.

Inclusion criteria were age >18 years and FXIII values under the normal range (≤70%). Exclusion criteria were bleeding disorders other than FXIII and not fulfilling the inclusion criteria. We enrolled 104 patients in this analysis. Demographic data and laboratory parameters, as well as the number of blood products and pro-coagulatory substances given during the period of intensive care, were evaluated. The follow-up ended with Dismissal from intensive care unit.

Statistical data were collected with an electronic database system (Microsoft Excel®, Microsoft Deutschland GmbH, Unterschleißheim). The statistical analysis and figures were

Table 1. Patient Characteristics of the Analyzed Cohort.

Parameter	Median (min-max)
Age [years]	57 (18-86)
Weight [kg]	67.7 (34-130)
Lowest FXIII Level [%]	47.4 (18.8-69.8)
Lowest Prothrombin Time [%]	51.5 (7-117)
Highest aPTT [sec]	58.5 (27-180)
Lowest Fibrinogen Level [mg/dL]	177 (60-834)
Lowest FVIII-Level [%]	136.5 (62-400)
Lowest Hemoglobin Level [g/dL]	7.6 (4.6-14.9)
Highest Hemoglobin Level [g/dL]	13.7 (10.4-19.6)
Packed Red Blood Cells (U)	24 (2-122)
Fresh Frozen Plasma (U)	17 (1-60)
PPSB (IU)	4800 (600-57600)
Thrombocyte Concentrates (U)	10 (2-195)
Given Fibrinogen (g)	6 (1-68)
Antithrombin-III (IU)	6000 (500-54500)
FXIII-Substitution (IU)	2500 (1250-51250)

performed with SPSS (Statistical Product and Services Solutions, Version 25, SPSS Inc., Chicago, IL, USA) and Graphpad Prism (Version V, GraphPad Software, La Jolla, USA Graph Pad). Descriptive statistics were carried out for the complete dataset. The Student's t-test and one-way Anova with Kruskal-Wallis, as well as the Dunns-Multiple Comparison and Mann-Whitney-U Test, were used for the determination of significance (*= $P < 0.05$, **= $P < 0.01$, ***= $P < 0.001$).

Results

In total, 104 individuals divided in 38 female and 66 male patients were included in the present retrospective analysis of patients with mild FXIII deficiency (≤70%) treated at the ICU. The lowest FXIII levels measured ranged from 18.8% to 70% (Table 1).

The patient collective was separated by different causes of stay at the ICU, differentiated between major interventions (e.g., abdominal, heart, vascular surgery; $n = 39$), minor interventions (e.g., gastroscopy, tonsillectomy, drains; $n = 9$), primary trauma ($n = 12$), and a spontaneous bleeding event ($n = 24$). There was no statistical difference in FXIII activity levels between the analyzed groups regarding the cause of ICU stay ($P = 0.8375$).

The lowest FXIII levels were also compared by the bleeding focus in the 6 different groups: Abdominal, Head/ Neck, Trauma, Gynecology, Vascular, and Others. Visually, the results indicate higher minimum FXIII values for a Head/ Neck or Gynecology Focus. In comparison, patients with an abdominal focus in particular had significantly lower values of FXIII (Abdominal vs. Head/ Neck $P < 0.05$, Abdominal vs. Gynecology $P < 0.05$, $P = 0.0027$) (Figure 1).

In Figure 2, the patient collective is shown separated by the need of any kind of blood products. The graph demonstrates that the median FXIII value was significantly lower in the patients treated with blood products compared to the group without any transfusion (41.3% vs. 57.9%; $P < 0.001$).

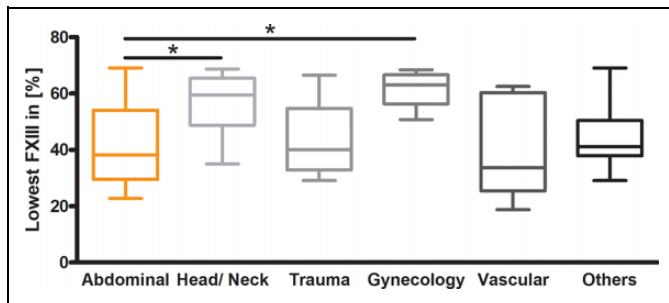


Figure 1. Lowest measured factor XIII activity related to focus of illness. Comparison of different illness foci: abdominal ($n = 37$), head/neck ($n = 13$), trauma ($n = 12$), gynecology ($n = 5$), vascular ($n = 7$), others ($n = 8$). The Kruskal-Wallis test was performed with $P = 0.0027$, Dunn's Multiple Comparison test is indicated by $*=P < 0.05$.

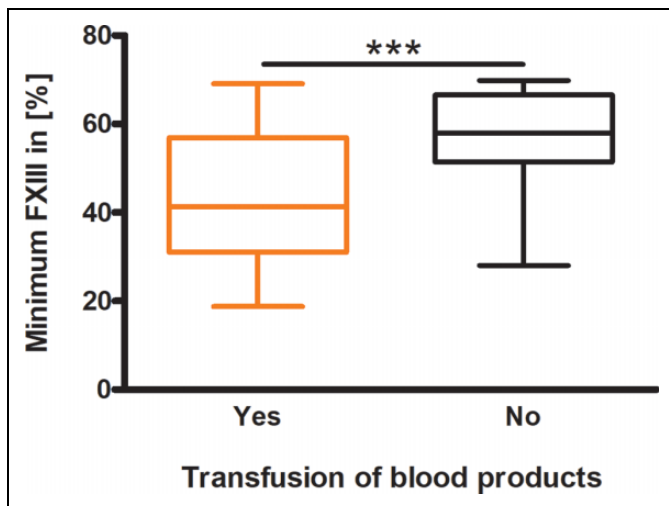


Figure 2. Differences in factor XIII activity divided by need of transfusion. Patients who needed a transfusion during ICU stay were compared with those who did not receive blood products at any time ($n = 83$ vs. $n = 21$); the Student's t-test was performed with $P = 0.0003$. $P < 0.001 = ***$.

To evaluate the clinical relevance of a mild deficiency, different FXIII cut-off values were defined. Afterwards, the patient collective was separated by the varying FXIII cut-offs and the groups were compared with their clinical course. The cut-offs of 60% (<60 $n = 78$, $\geq 60\%$ $n = 26$), 50% (<50 $n = 56$, $\geq 50\%$ $n = 48$), 40% (<40 $n = 39$, $\geq 40\%$ $n = 65$), and 30% (<30 $n = 20$, $\geq 30\%$ $n = 84$) were analyzed.

We also compared the different FXIII cut-offs with other standard coagulation parameters. The global coagulation parameters of maximum activated partial thromboplastin time (aPTT) ($P = 0.0003$), minimum prothrombin time ($P = 0.0001$), and minimum fibrinogen level (not shown, $P = 0.0004$) showed significant differences between patients with FXIII values above and below 60% (Figure 3A and B), indicating a global impact on coagulation systems with a hampered pro-coagulatory capacity. Interestingly, FVIII values were not different between the groups (not shown, $P = 0.8713$).

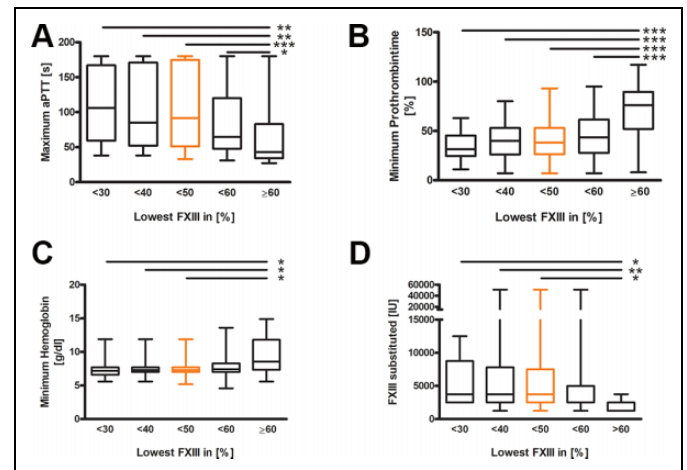


Figure 3. Comparison of factor XIII activity cut-offs. A and B, Comparing the different groups of minimum factor XIII activity levels shows that the standard coagulation parameters max. partial thromboplastin time (<30 $n = 20$, <40 $n = 39$, <50 $n = 56$, <60 $n = 78$, ≥ 60 $n = 24$; spearman $R2 = -0.34$, $P = 0.001$) and min. prothrombin time (<30 $n = 20$, <40 $n = 39$, <50 $n = 56$, <60 $n = 78$, ≥ 60 $n = 26$; Spearman $R2 = 0.49$, $P < 0.001$) correlate negatively and positively with the minimum FXIII activity, respectively. C, Shows the minimum hemoglobin values (<30 $n = 20$, <40 $n = 39$, <50 $n = 56$, <60 $n = 78$, ≥ 60 $n = 26$) that differ significantly beginning at FXIII $<50\%$ compared to $\geq 60\%$. D, The substitution of FXIII units is shown for the different groups of minimum FXIII activity level (<30 $n = 11$, <40 $n = 22$, <50 $n = 30$, <60 $n = 43$, ≥ 60 $n = 9$). The Kruskal-Wallis test was performed; Dunn's Multiple Comparison test is indicated by $P < 0.05 = *$, $P < 0.01 = **$, $P < 0.001 = ***$.

The mentioned difference in FXIII levels between patients with and without transfusion could also be shown vice-versa. Comparing the groups with FXIII levels $\geq 60\%$ and the other cut-offs results in significantly lower minimum hemoglobin values beginning at $<50\%$ ($P = 0.0125$) (Figure 3C). The maximum hemoglobin level did not differ between the different analyzed cut-offs of FXIII (not shown). However, in the patients with FXIII cut-off values $<50\%$, significantly more units of FXIII had been substituted ($P < 0.005$) (Figure 3D).

Despite the differences in laboratory clotting tests, the pro-coagulatory management over time was quite similar: the amounts of PPSB, fibrinogen and AT-III (not-shown) given did not differ between the groups (Figure 4A and B).

This also correlates with the number of given packed red blood cells (PRBC), which was higher in patients with FXIII Levels $<50\%$ ($P = 0.0421$) (Figure 5A). On the other hand, there was no difference in the amount of FFP given to patients of the different cut-offs ($P = 0.1916$) (Figure 5B).

Table 2 shows the characteristics of the patient collective separated by a 50% cut-off for the lowest measured FXIII value. Patients with FXIII levels <50 received significantly more FXIII-products. There is a slight difference in age between the groups, but no statistically significant difference in body weight. The minimum and maximum hemoglobin values measured were significantly lower in patients with FXIII $<50\%$; consequently, the rate of PRBC transfusions was higher

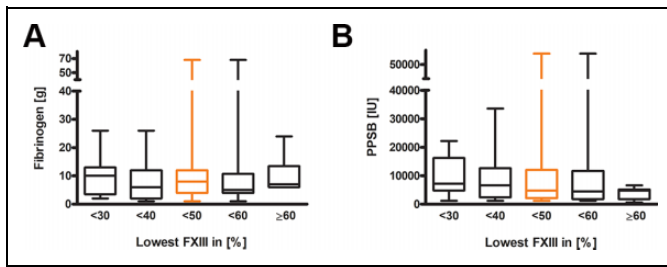


Figure 4. Amount of substituted clotting factors for different minimal factor XIII activity cut-offs. (A) Shows the substitution of fibrinogen (<30 n = 10, <40 n = 17, <50 n = 27, <60 n = 36, ≥60 n = 6) and (B) shows PPSB (<30 n = 11, <40 n = 19, <50 n = 29, <60 n = 34, ≥60 n = 7) compared between groups with different minimum FXIII activities and ≥60 % minimum FXIII activity. The Kruskal-Wallis test was performed; Dunn's Multiple Comparison test is indicated by $P < 0.05 = *$, $P < 0.01 = **$, $P < 0.001 = ***$.

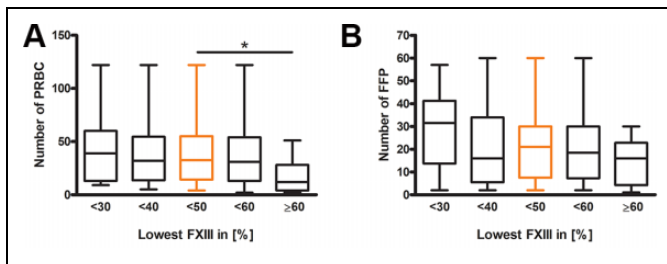


Figure 5. Amount of blood transfusions for different minimal factor XIII activity cut-offs. (A) Shows the substitution of packed red blood cells (PRBC) (<30 n = 19, <40 n = 37, <50 n = 52, <60 n = 65, ≥60 n = 15) and (B) fresh frozen plasma (FFP) (<30 n = 16, <40 n = 33, <50 n = 45, <60 n = 52, ≥60 n = 12) compared between groups with different minimum FXIII activities and ≥60 % minimum FXIII activity. The Kruskal-Wallis test was performed; Dunn's Multiple Comparison test is indicated by $P < 0.05 = *$, $P < 0.01 = **$, $P < 0.001 = ***$.

in this group. Similarly, the measured coagulation parameters also differed significantly between the collectives, but management with pro-coagulatory substances, like fibrinogen, PPSB, AT-III, and FFP, showed no differences. The rate of thrombocyte transfusion also showed no group difference.

Discussion

Clinical data suggest that mild FXIII deficiency is an underdiagnosed and underrepresented disease entity that is common in the perioperative setting. The analysis of Lawrie et al, with a sample of >1000 patients, showed that 21% of the hospitalized patients had a FXIII activity out of the normal range (<70%), and 6% reached values <50%.²⁹ Some publications suggest that there is no correlation between FXIII activity and bleeding events or transfusion of blood products.^{30,31} However, Rappard et al demonstrated that FXIII was the most important independent variable of clot firmness, and in different studies the preoperative treatment with FXIII (FXIII activity target >70%) significantly reduced the need of transfusion as well as the perioperative blood loss.³²⁻³⁴

The results of the present analysis of 104 patients with mild FXIII deficiency strengthen the clinical relevance of FXIII in the intensive care setting and support the association between FXIII activity and transfusion of blood products (Figure 2). Comparing the different groups of patients, those with lower FXIII levels, beginning at <60%, showed lower minimum and maximum hemoglobin values (Figure 3C). Furthermore, our data support the results of Song et al that a reduced FXIII activity correlates significantly with general coagulation markers, such as prothrombin time, aPTT, and fibrinogen which show reduced values for lower FXIII levels (Figure 3A and B).³⁵ These comparisons match with the finding, that in the underlying analysis the patients with FXIII activities <50% had a significantly higher need for PRBC Transfusion (Figure 5), even though the amount of given FFP, thrombocytes, PPSB, AT-III, and fibrinogen did not differ (Table 2).

To classify these results the (patho-)physiology of FXIII plays an important role. The symptoms of mild FXIII deficiency consist of delayed bleeding events, occurring 12-36 h after a trauma, probably caused by a reduced clot firmness, which correlates with FXIII activity and early fibrinolysis by a lack of alpha-2 plasmin inhibitor crosslinking.^{10,11,15} A previous study actually indicates that cross linking requires FXIII activity levels of at least 30%, but is completed only at much higher levels.³⁶ This could be an indicator that mild FXIII deficiency, as analyzed in the present study, particularly plays a role in disseminated minor bleeding events, which become clinically relevant after a longer period of bleeding. This hypothesis correlates with the results of another study, showing that patients with mild FXIII deficiency had higher drainage volumes postoperatively.³⁷

Comparing the amount of FXIII substitution in the present study between the groups of FXIII activities below and over 50%, patients with lower FXIII levels were consequently substituted with 3 times more units of FXIII (Figure 3D). Since further there has been no difference in the need for pro-coagulatory treatment between the 2 groups, the higher rate of PRBC transfusion in the patients with FXIII <50% must be explained otherwise. Taking into consideration, that the half-life of FXIII is about 10-12 days, this could be a sign of a higher FXIII consumption, e.g. in the case of prolonged bleeding or as part of disseminated intravascular coagulopathy, an effect that has already been described.^{35,38,39}

The results of the underlying analysis further suggest that the cause of bleeding, compared between spontaneous events, trauma, and major or minor surgery, has no influence on the lowest measured FXIII activity. More important seems to be the focus of illness and/or bleeding event. Patients with an abdominal focus showed significantly lower FXIII activities than head/neck or gynecological foci (Figure 1).

Limitations of this study are the retrospective design, which is only able to generate new hypotheses, and the fact that there were just minimum and maximum values of FXIII activities, but no repeated measurements for the complete period of ICU stay. Nevertheless, a minimum FXIII activity below 50% measured at any point in the course of the disease was associated with a significantly higher need for PRBC transfusion. In the

Table 2. Patient Characteristics Comparing Minimum FXIII Activity <50% and ≥50%.^a

	Lowest factor XIII level <50%, mean (min-max)	Lowest factor XIII level ≥50%, mean (min-max)	Significance level ^b
Age [years]	59 (19-86)	50 (18-79)	0.0103
Weight [kg]	70.6 (34-130)	74.1 (52-113)	0.5563
Lowest FXIII Level [%]	35 (18.8-49.6)	61 (50-70)	<0.0001
Lowest Prothrombin Time [%]	40 (7-93)	66 (8-117)	<0.0001
Highest aPTT [sec]	104 (33-180)	63 (27-180)	<0.0001
Lowest Fibrinogen Level [mg/dL]	163.0 (60-600)	227.8 (60-837)	0.0005
Lowest FVIII-Level [%]	177 (62-400)	176 (81-395)	0.6635
Lowest Hemoglobin Level [g/dL]	7.6 (5.2-11.9)	9.1 (4.6-14.9)	0.0044
Highest Hemoglobin Level [g/dL]	13.4 (10.4-17.4)	14.3 (11.3-17.1)	0.0046
Packed Red Blood Cells (U)	40.48 (4-122)	21 (2-64)	0.0017
Fresh Frozen Plasma (U)	21 (2-60)	17 (1-60)	0.2278
PPSB (IU)	9282 (1200-57600)	6750 (600-44400)	0.2041
Thrombocytes Concentrates (U)	19 (2-195)	11 (2-36)	0.1280
Given Fibrinogen (g)	10.5 (1-68)	8.5 (2-39)	0.3408
Antithrombin-III-Subst. (IU)	11286 (500-54500)	9208 (2000-35500)	0.7309
FXIII-Substitution (IU)	6417 (1250-51250)	2102 (1250-3750)	0.0002

^aStatistical analysis was performed with the Mann-Whitney-U-test.

^bBoldface values correspond to significant results with $P < 0.05$.

patient groups with FXIII levels <40% and <30% there was only a non-significant trend toward a higher need for PRBC transfusion, probably because the analysis was under-powered due to the reduced number of patients in these groups (Figure 5).

Further prospective randomized studies are needed to confirm these results and strengthen the evidence regarding the clinical relevance of mild acquired FXIII deficiency.

Conclusion

Taken together, these results indicate that a mild FXIII deficiency occurring at any point of ICU stay is also probably relevant for the total need of PRBC, independent of pro-coagulatory management, which did not differ between the groups. Based on the underlying data and the literature, it is important raising awareness of mild FXIII deficiency in the intensive care setting and we recommend providing routine measurements in patients at high risk of bleeding. At present, in alignment with the ESAIC guidelines, an early management with the substitution of FXIII at levels <50-60% could be suggested.^{32,40}

Abbreviations

aPTT	activated partial thromboplastin time
FXIII	Factor XIII
FFP	fresh frozen plasma
PRBC	packed red blood cells.

Authors' Note


F.C.F. Schmitt and M. von der Forst share first authorship and contributed equally. F.C.F. Schmitt: First author equal contribution, Analysis and Interpretation of Data, Supervision, Writing—Original Draft. M. von der Forst: First author equal contribution, Analysis and Interpretation of Data, Visualization, Writing - Original Draft. W. Miesbach: Study Conception and Recruitment. S. Casu: Study Design,

Methodology and Proof Reading. M.A. Weigand: Interpretation of Data and Writing—review & editing. S. Alesci: Conceptualization and Recruitment, Writing—review & editing; No conflicts of interest. This article has been professionally proofread by Proof-reading-service.com Ltd. Devonshire, Business Center, Works Road, Letchworth Garden City, Hertfordshire, SG6 1GJ, United Kingdom. The study has been approved by the local ethics committee of the Goethe-University of Frankfurt am Main (Nr. 222/12). Written informed consent was obtained from the patient or a legally authorized person for their anonymized information to be published in this article.

Declaration of Conflicting Interests

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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