




BRIEF REPORT

Influence of blood group, von Willebrand factor levels, and age on factor VIII levels in non-severe haemophilia A

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Abstract

Background: Data on the effect of ABO blood group (ABO), von Willebrand factor (VWF) levels, and age on factor VIII (FVIII) in non-severe haemophilia A (HA) is scarce. **Objective:** To investigate if ABO, VWF levels, and age have an influence on the variability of FVIII levels and consequently on the assessment of severity in non-severe HA. **Patients/Methods:** Eighty-nine patients with non-severe HA and 82 healthy controls were included. Data on ABO was collected and FVIII clotting activity (FVIII:C) with one-stage clotting assay (FVIII:C OSA) and chromogenic substrate assay (FVIII:C CSA), FVIII antigen (FVIII:Ag) and VWF antigen (VWF:Ag) and activity (VWF:Act) were determined. **Results:** In HA, FVIII:C OSA and CSA and FVIII:Ag were not different between non-O (n = 42, median 15.5, interquartile range 10.4-24.0; 10.0, 6.8-26.0 and 15.2, 10.7-24.9) and O (n = 47, 14.1, 9.0-23.0; 10.0, 5.0-23.0 and 15.2, 9.3-35.5), whereas in healthy controls, non-O individuals had significantly higher FVIII levels. FVIII:C showed no relevant correlation with VWF levels in HA, but we observed strong correlations in healthy controls. Age had only a minor influence in HA, but had a considerable impact on FVIII:C in healthy controls. In multivariable regression analysis ABO, VWF:Ag and age were not associated with FVIII:C in HA, whereas this model explained 61.3% of the FVIII:C variance in healthy controls. **Conclusions:** We conclude that in non-severe HA ABO and VWF levels do not substantially influence the variability of FVIII levels and age has only minor effects on it, which is important information for diagnostic procedures.

KEYWORDS

ABO blood-group system, diagnostic techniques and procedures, factor VIII, haemophilia A, von Willebrand Factor

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1 | INTRODUCTION

Blood coagulation factor VIII (FVIII) circulates in blood bound to von Willebrand factor (VWF). This binding stabilizes and protects FVIII from decay.¹⁻³ Persons with ABO non-O have 25%-35% higher levels of VWF and FVIII than persons with O,⁴⁻⁷ which is accompanied by longer FVIII half-life in haemophilia A (HA).³ VWF and FVIII levels also increase with age.^{6,8}

The effects of ABO and age on FVIII are at least partially mediated through VWF. Kamphuisen et al investigated female relatives of HA patients.⁹ ABO non-O and higher age were associated with higher FVIII clotting activity (FVIII:C) and VWF antigen (VWF:Ag) levels in both carriers and non-carriers of F8 mutations, which remained after correction for VWF:Ag.⁹ Orstavik et al found that the impact of ABO and age on FVIII:Ag levels was secondary to the impact on VWF:Ag in persons without bleeding symptoms.⁸ Ay et al analyzed FVIII and VWF levels in carriers of HA and healthy controls. They found that ABO influenced VWF, but not FVIII:C in carriers, whereas the ABO affected VWF and FVIII:C in healthy controls.¹⁰

The role of ABO, VWF levels, and age in FVIII variability in non-severe HA has not been explored in detail, but could be important for diagnosis.¹¹ Therefore, we aimed to investigate if ABO, VWF, and age influence the variability of FVIII:C in non-severe HA.

2 | PATIENTS AND METHODS

Patients with HA (≥ 18 years of age) with baseline FVIII:C of 1%-40%¹² were included in this observational, cross-sectional study of four Austrian haemophilia centers within the framework of the Austrian haemophilia registry.¹³ The lowest FVIII level ever measured in patients' history served as the basis for the diagnosis and assessment of severity. Mild and moderate haemophilia was defined according to the recommendations from the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH).¹² Exclusion criteria were platelet count $< 100 \times 10^5/L$, restricted renal or hepatic function (prothrombin time $< 75\%$ of normal levels or serum creatinine > 2.0 mg/dL), active malignancy, surgery within the last 6 weeks, overt infection within the last 2 weeks, or inhibitor against FVIII. All patients were of Caucasian descent. Blood samples were collected during a routine visit after obtaining written informed consent.

Eighty-two healthy men were recruited as healthy controls at the Division of Haematology and Haemostaseology of the Medical University of Vienna. All healthy controls had negative bleeding history and provided written informed consent.

All study procedures were approved by the local ethics committees.

ABO had been previously determined and information was gained from patients' files. We determined the following

Essentials

- ABO, von Willebrand factor (VWF), and age influence factor VIII (FVIII) levels in the general population.
- We investigated the impact of ABO, VWF levels, and age in non-severe haemophilia A (HA) patients.
- Neither ABO nor VWF had a remarkable influence on FVIII levels in non-severe HA; age had a minor influence.
- For the assessment of baseline FVIII variability, ABO and VWF need not be taken into account.

parameters: FVIII:C one-stage clotting assay (OSA; native FVIII-deficient plasma – Technoclone and Aktin FS activator – Siemens), VWF activity (VWF:Act; BC von Willebrand Reagent or Innovance VWF Ac – Siemens), and VWF:Ag (STA LIATEST VWF, Diagnostica Stago). In HA we additionally measured FVIII clotting activity chromogenic substrate assay (FVIII:C CSA; TECHNOCHROM FVIII:C, Technoclone) and FVIII:Ag (VisuLize FVIII Antigen Kit, Affinity Biologicals). Molecular analysis of the F8 gene had previously been performed in all patients.

As levels of VWF and FVIII were not normally distributed we performed Mann-Whitney-U test to compare groups and Spearman's test to investigate correlations. We analyzed the associations among ABO, age, VWF, and FVIII levels by univariable and multivariable linear regression. A two-tailed *P*-value $< .05$ was considered statistically significant. Spearman's rho of -0.3 to 0.3 was considered non-relevant, -0.3 to -0.5 and 0.3 to 0.5 weak, -0.5 to -0.7 and 0.5 to 0.7 moderate, and -0.7 to -1.0 and 0.7 to 1.0 strong correlation coefficients.^{14,15} For statistical analysis we used the Statistical Package for Social Sciences (SPSS IBM Version 25.0).

3 | RESULTS AND DISCUSSION

We included 89 patients with non-severe HA and 82 healthy men. Median age was 51 years (interquartile range [IQR] 37-61) in HA and 48 (IQR 32-56) in healthy controls (*P* = .447).

Forty-two patients had ABO non-O (47.2%) and 47 had O (52.8%). There were 50 healthy controls with ABO non-O (61.0%) and 32 with O (39.0%). Blood group O was more frequent (*P* = .015) in HA.

In four HA patients no mutation was found in the exons, the adjacent intronic regions, the 5'UTR, and the 3'UTR of the F8 gene; in these patients von Willebrand disease type 2N was excluded. In the other 85 HA patients 46 different F8 mutations were present; the majority (*n* = 43) were missense mutations including six mutations that have not been described previously.

There was no significant difference in FVIII:C OSA and CSA, FVIII:Ag between non-O and O HA patients (Table 1, Figure 1A), whereas non-O HA patients had significantly higher levels of

TABLE 1 Distribution of laboratory parameters according to ABO blood group non-O and O in patients with haemophilia A (n = 89) and healthy controls (n = 82)

Haemophilia A patients	Non-O ^a (N = 42)	O ^a (N = 47)	P-value
FVIII:C OSA (%)	15.5; 10.4-24.0	14.1; 9.0-23.0	.687
FVIII:C CSA (%)	10.0; 6.8-26.0	10.0; 5.0-23.0	.619
FVIII:Ag (%)	15.2; 10.7-24.9 ^b	15.2; 9.3-35.5 ^c	.767
VWF:Ag (%)	126.5; 102.0-178.0	103.0; 82.0-133.0	.002
VWF:Act (%)	123.0; 94.5-163.0 ^b	87.0; 75.0-110.0	.002
Healthy controls	Non-O ^a (N = 50)	O ^a (N = 32)	P-value
FVIII:C OSA (%)	150.0; 123.8-180.5	109.5; 99.0-127.0	<.001
VWF:Ag (%)	126.0; 104.5-161.0	86.0; 70.3-103.3	<.001
VWF:Act (%)	117.0; 86.0-148.0 ^d	71.0; 60.0-96.0 ^e	<.001

Note: FVIII:C CSA, factor VIII chromogenic substrate assay; FVIII:C OSA, factor VIII one-stage clotting assay; FVIII:Ag, factor VIII antigen; non-O, ABO blood group non-O; O, ABO blood group O; VWF:Ag, von Willebrand factor antigen; VWF:Act, von Willebrand factor activity.

A P-value of <.05 was considered to be significant

^aValues in median; interquartile range,

^bN = 40

^cN = 43

^dN = 49

^eN = 31

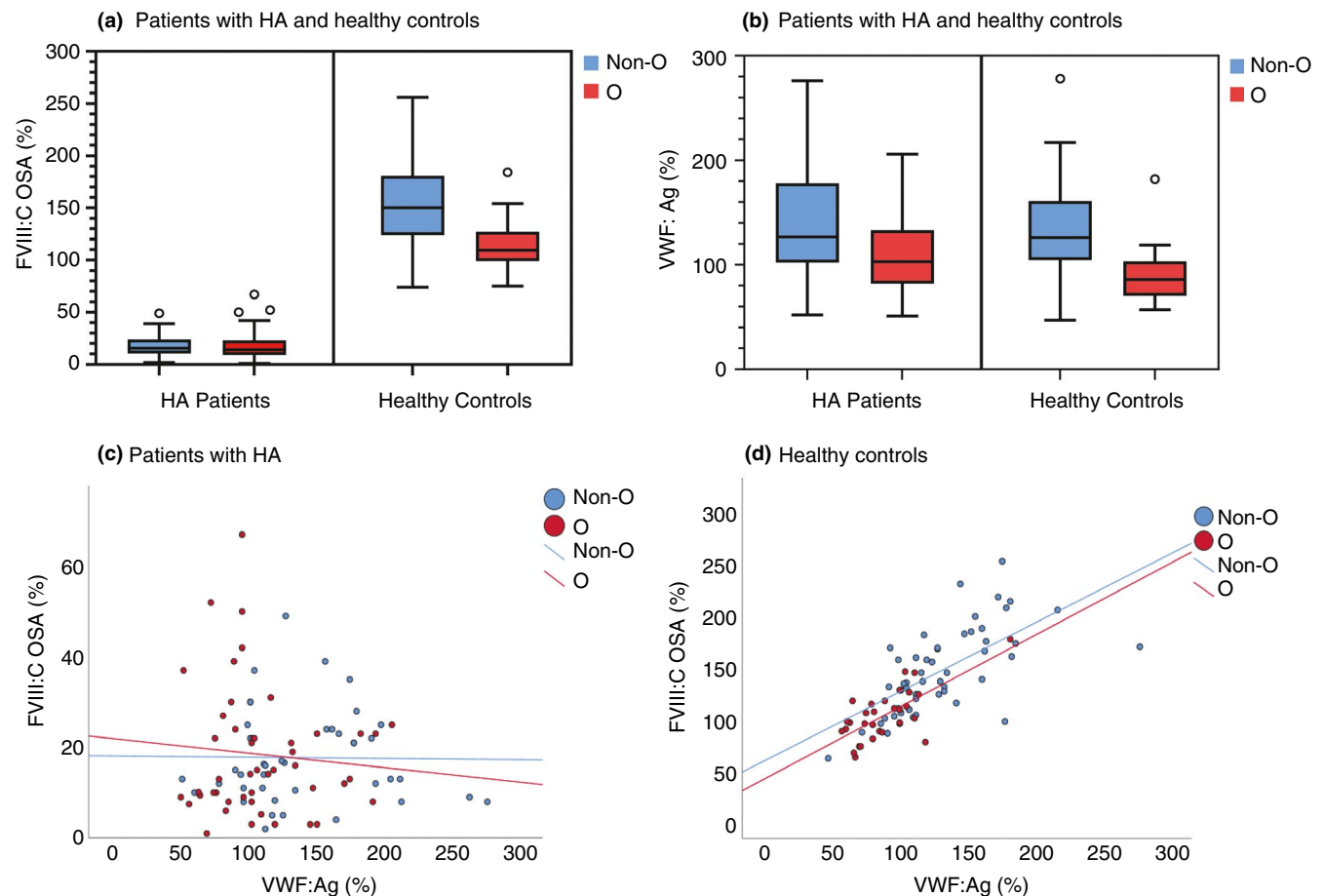


FIGURE 1 FVIII:C OSA and VWF:Ag levels according to ABO blood group non-O and O in patients with non-severe haemophilia A (HA; n = 89) and in healthy controls (n = 82). A and B, The boxes depict the interquartile range (IQR), the whiskers the largest or smallest value no farther from the upper or lower end of the box than 1.5*IQR. Outliers are values beyond the end of the whiskers and marked by rings. C and D, FVIII:C OSA versus VWF:Ag in HA patients (C) and healthy controls (D). FVIII:C OSA, Factor VIII one-stage clotting assay; HA, haemophilia A; non-O, ABO blood group non-O; O, ABO blood group O; VWF:Ag, von Willebrand factor antigen

VWF:Ag and VWF:Act (Table 1, Figure 1B). In the control group, VWF:Ag, VWF:Act, and FVIII:C levels were significantly higher in non-O individuals (Table 1, Figure 1A and B).

Next, we investigated if FVIII correlated with VWF. In HA there was no correlation of FVIII:C OSA with VWF:Ag or with VWF:Act. FVIII:C CSA and FVIII:Ag were not correlated with VWF:Ag and non-relevantly correlated with VWF:Act (Table 2). In univariable linear regression in HA there was no association between FVIII:C OSA with VWF:Ag ($R^2 = .003$, $P = .588$) or VWF:Act ($R^2 = .001$, $P = .789$) or of FVIII:C CSA with VWF:Ag ($R^2 = .003$, $P = .617$) and VWF:Act ($R^2 = .025$, $P = .145$). A scatter plot of FVIII:C OSA and VWF:Ag with regression line is shown in Figure 1C. The relationship between FVIII:C OSA and VWF:Ag levels was analyzed in the three biggest groups with identical F8 mutations, one comprising nine and two with seven patients. We found strong associations after excluding one outlier from one of the groups with seven patients. In univariable linear regression P -values were between .001 and <.0001, R^2 between .890 and .966, and 1% increase in the VWF:Ag was associated with 0.12%-0.13% increase in the FVIII:C OSA.

In healthy controls we observed strong correlations of FVIII:C OSA with VWF:Ag and VWF:Act (Table 2). In healthy controls a 1% elevation in the VWF:Ag was associated with an 0.73% elevation in the FVIII:C ($R^2 = .558$, $P < .001$) and a 1% elevation in the VWF:Act with an 0.77% elevation in the FVIII:C ($R^2 = .556$, $P < .001$). In Figure 1D a scatter plot of FVIII:C OSA and VWF:Ag with regression line for healthy controls is shown.

We investigated if age impacted FVIII and VWF levels. In HA patients we found a non-relevant correlation of FVIII:C OSA with age, no significant correlation of FVIII:C CSA, and a weak positive correlation of FVIII:Ag with age (Table 2). VWF:Ag and VWF:Act showed weak positive correlations with age in HA (Table 2). In healthy controls there were non-relevant to weak correlations of FVIII:C OSA, VWF:Act, and VWF:Ag with age (Table 2). In univariable linear regression age was not associated with FVIII:C OSA ($R^2 = .024$, $P = .151$) in HA (Figure 2A). When non-O and O healthy controls were analyzed separately regarding the association of FVIII:C OSA with age, a significant association was only observed in non-O ($R^2 = .265$, $P < .001$), in which age explained 26.5% of the variance in FVIII:C and in which FVIII:C increased by 1.26% per year (Figure 2B). In ABO O FVIII:C was not associated with age ($R^2 = .031$, $P = .337$, Figure 2B).

In multivariable linear regression we investigated if FVIII:C OSA was associated with ABO, VWF:Ag, and age. In HA patients we found no significant association ($P = .273$). However, in healthy controls the association between ABO, VWF:Ag, age, and FVIII:C was significant ($P < .001$) and explained 61.3% of the FVIII:Act variance.

It has been convincingly shown that ABO, VWF levels, and age are important determinants of FVIII levels in the general population.^{4,5,8} In our analysis we systematically evaluated the influence of ABO, VWF, and age on FVIII in non-severe HA patients and healthy controls. We did not find any difference in FVIII:C OSA or CSA or FVIII:Ag levels in

TABLE 2 Correlations among VWF levels, FVIII levels, and age in patients with haemophilia A ($n = 89$) and healthy controls ($n = 82$)

	VWF:Ag	VWF:Act	Age
Haemophilia A			
FVIII:C OSA			
Spearman's rho	0.028	0.180	0.215
P -value	.795	.095	.043
N	89	87	89
FVIII:C CSA			
Spearman's rho	0.120	0.253	0.203
P -value	.265	.018	.057
N	89	87	89
FVIII:Ag			
Spearman's rho	0.112	0.226	0.311
P -value	.312	.042	.004
N	83	81	83
VWF:Ag			
Spearman's rho	-	-	0.459
P -value	-	-	<.001
N	-	-	89
VWF:Act			
Spearman's rho	-	-	0.420
P -value	-	-	<.001
N	-	-	87
Healthy controls			
FVIII:C OSA			
Spearman's rho	0.790	0.751	0.292
P -value	<.001	<.001	.008
N	82	80	82
VWF:Ag			
Spearman's rho	-	-	0.281
P -value	-	-	.011
N	-	-	82
VWF:Act			
Spearman's rho	-	-	0.339
P -value	-	-	.002
N	-	-	80

Note: FVIII:Ag, factor VIII antigen; FVIII:C CSA, factor VIII chromogenic substrate assay; FVIII:C OSA, factor VIII one-stage clotting assay; VWF:Ag, von Willebrand factor antigen; VWF:Act, von Willebrand factor activity.

A P -value of <.05 was considered to be significant.

Spearman's rho of -0.3 to 0.3 was considered to be non-relevant, -0.3 to -0.5 and 0.3 to 0.5 was considered weak, -0.5 to -0.7 and 0.5 to 0.7 was considered moderate, and -0.7 to -1.0 and 0.7 to 1.0 was considered to be a strong correlation coefficient.

non-O patients compared to O. The correlations between FVIII and VWF can be regarded as non-relevant, as we found no or only very weak correlations. There was a consistent but also very weak correlation with age. Whereas in healthy controls more than 60% of the

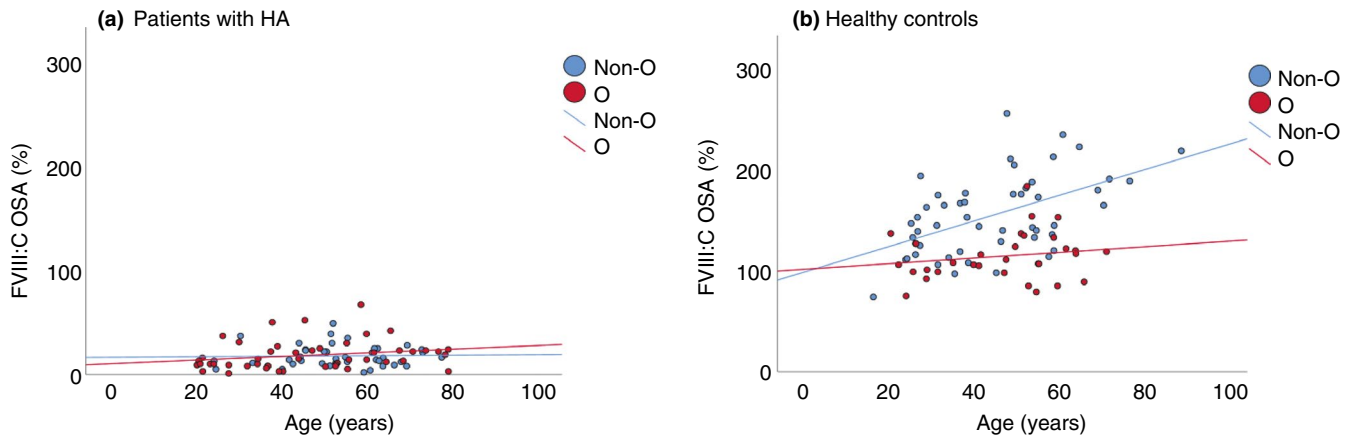


FIGURE 2 FVIII levels according to age in non-severe haemophilia A ($n = 89$, A) and in healthy controls ($n = 82$, B). FVIII:C OSA, Factor VIII one-stage clotting assay; non-O, ABO blood group non-O; O, ABO blood group O

variance in FVIII:C could be explained by ABO, VWF:Ag, and age, no significant association with these parameters could be found in HA.

To our knowledge only one study has hitherto investigated the impact of ABO on FVIII levels in non-severe HA. This study from the INSIGHT group¹⁶ did not find a difference between FVIII:C OSA in ABO non-O versus O in non-severe HA. In the same publication VWF was evaluated in a subgroup of patients with FVIII:C and VWF measurements on the same day and no association could be found. When baseline FVIII and VWF levels were compared in a group of patients with identical F8 mutation, a correlation was found ($P = .003$).

Delbrück et al¹⁷ investigated 48 mild, 10 moderate, 7 severe patients with HA, and 23 carriers of HA regarding the association of FVIII:C with VWF:Ag, VWF:Ristocetin Cofactor (VWF:RCo), and age. In mild HA they observed a significant increase in FVIII:C with age and no association in moderate HA. For calculating the associations between FVIII:C and VWF levels data of patients with HA of all severities and carriers were merged. A significant association of FVIII:C with VWF:RCo and no association of FVIII:C with VWF:Ag were observed. For calculating the associations, multiple measurements from single subjects were used.

Miesbach et al investigated the influence of age on FVIII:C¹⁸ over a period of median 17 years. A significant correlation between FVIII levels and age was observed in 29 patients with mild HA. One study that investigated the influence of age in non-severe HA was published only as an abstract.¹⁹ In this longitudinal retrospective study there was no observable trend of FVIII with time in the analysis of the whole cohort, but only in those with a baseline FVIII:C level of <15 IU/dL.

Albáñez et al described the relationship between age and FVIII levels in 207 healthy individuals.²⁰ FVIII levels increased significantly with age both in non-O and O individuals, but aging was more strongly associated with FVIII levels in non-O. We found that aging only increased FVIII:C significantly in non-O healthy controls and the degree of increase was higher in our cohort of non-O individuals than that of Albáñez et al. A possible explanation for this difference is that our cohort was smaller and we included only adults whereas Albáñez et al included children as well.

Our study has the limitation that we included only patients who were not acutely ill at the time of blood sampling. Thus, we cannot comment on the effect of VWF on FVIII during acute phase reaction. This study is unique with regard to the fact that we simultaneously investigated the important, potentially influencing factors ABO, VWF, and age. Major strengths of our study are that we assessed not only FVIII:C OSA but also FVIII:C CSA and FVIII:Ag levels in HA, which has not been done before. The inclusion of the control group allowed direct comparisons between patients with HA and the general population.

Our data, together with data from the literature, exclude a major influence of ABO on FVIII level in non-severe haemophilia A. In patients with identical F8 mutation VWF seems to impact FVIII:C levels. However, in clinical practice patients are not stratified according to F8 mutations, because of the high number of causative F8 mutations, so in non-severe HA overall, only minor influences of VWF can be assumed, which were clearly lower in comparison to the impact of VWF on FVIII levels in healthy individuals. Age has a significant but much less important influence in HA compared to the general population. The most probable explanation for these results is that the mutations in the F8 gene have the most substantial impact on FVIII levels compared to the other factors.¹⁶

We conclude that for the assessment of FVIII levels in patients with mild or moderate haemophilia A neither the ABO, nor the VWF level, have to be taken into account. Age has to be considered a minor modification factor, as there is a consistent, but weak, increase in FVIII levels with age. These aspects are important in daily practice, when a diagnosis of non-severe haemophilia A has to be made.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

I. Pabinger, J. Rejtő, and O. Königsbrügge designed the study; I. Pabinger, C. Ay, J. Rejtő, G. Schuster, C. Feistritzer, S. Hofer, and L. Mauracher recruited patients; P. Quehenberger and R. Sunder-Plaßmann performed laboratory analysis; J. Rejtő, E. Grilz, and O. Königsbrügge performed statistical analyses; I. Pabinger, J. Rejtő, J. Gebhart, E. Grilz, O. Königsbrügge, and C. Gabler analyzed the data; I. Pabinger, J. Rejtő, O. Königsbrügge, J. Gebhart interpreted the data; J. Rejtő wrote the manuscript. All authors reviewed, edited, and approved the manuscript.

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