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ORIGINAL ARTICLE

The Impact of Human ABO Blood Groups on Thrombin Generation in Platelet-Poor Plasma

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SUMMARY

Background: **ABO blood group has been shown to influence plasma levels of von Willebrand factor (vWF) and factor VIII, contributing to individual variation in bleeding and thrombotic risk. Group O individuals typically present with lower vWF and factor VIII levels, associated with a higher bleeding tendency, whereas non-O groups tend to have elevated levels and an increased risk of thrombosis. However, it remains unclear whether ABO blood group also affects thrombin generation, a central parameter of coagulation potential.**
Methods: **We performed a retrospective analysis of 1,423 patients who underwent routine thrombin generation testing using a calibrated automated thrombogram (CAT) in platelet-poor plasma. Thrombin generation parameters, including lag time, peak thrombin, and endogenous thrombin potential (ETP), were compared across ABO blood groups (O, A, B, AB). Statistical differences between groups were assessed using ANOVA and post hoc comparisons, with a focus on potential clinical relevance.**
Results: **Statistically significant differences were observed in lag time and ETP between ABO blood groups. Group O individuals showed a slightly prolonged lag time and reduced total thrombin compared to non-O groups. However, the absolute magnitude of these differences was small, with median variations well within assay variability. Peak thrombin did not differ meaningfully between groups.**
Conclusions: **Although minor statistical differences in thrombin generation parameters were observed among ABO blood groups, their magnitude is unlikely to translate into clinically relevant effects. These findings suggest that the influence of ABO blood group on bleeding or thrombotic risk is not primarily mediated via changes in thrombin generation, but rather through vWF-related mechanisms such as platelet adhesion or clearance.**
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KEYWORDS

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INTRODUCTION

Thrombophilic disorders, such as the G1691A mutation in the factor V gene ('Factor V Leiden') and the prothrombin G20210 variant, are well-established risk factors for venous thromboembolism [1]. Genetic variants of this kind disrupt physiological anticoagulant pathways, resulting in increased clotting propensity.
Beyond hereditary mutations, the ABO blood group is now recognized as an important modulator of hemosta-

sis. Individuals with blood group O exhibit approximately 25% lower plasma levels of von Willebrand factor (vWF) and factor VIII compared to non-O groups [2, 3], which correlates with a higher propensity for bleeding. In contrast, non-O blood groups (A, B, AB) show elevated vWF and factor VIII levels that are associated with greater thrombotic risk [4,5]. These differential levels appear to result from variations in vWF glycosylation and clearance due to ABO(H) carbohydrate structures [5,6] and are reinforced by the expression of ABO antigens on platelets and endothelial cells, possibly affecting platelet adhesion and thrombin generation pathways independent of vWF [5].

A few small-cohort studies have noted a modest (~10%) reduction in thrombin generation among individuals with blood group O [7,8], but comprehensive data in large patient cohorts are lacking. Given the central role of thrombin generation in coagulation and its regulation by vWF and factor VIII, a systematic analysis across ABO blood groups is warranted.

In this study, we investigate the influence of ABO blood group on thrombin generation measured by calibrated automated thrombogram (TGA) in platelet-poor plasma and explore correlations with vWF, factor VIII, and key thrombin regulatory proteins.

MATERIALS AND METHODS

Patients were recruited from the patient cohort of the Coagumed Coagulation Center, Berlin, Germany, in a retrospective observational study conducted between January 2020 and December 2021. The study was approved by the Ethics Committee of the Medical School Brandenburg, Brandenburg an der Havel. All procedures adhered to the Declaration of Helsinki, and informed consent was obtained under institutional policy. The analysis included adult patients (≥ 18 years) who had undergone both ABO blood group determination and thrombin generation testing as part of routine diagnostic workup. Patients on anticoagulation with vitamin K antagonists or direct oral anticoagulants, as well as pregnant individuals, were excluded. Patients with incomplete datasets or missing blood group classification were not included. All data were processed pseudonymously in accordance with data protection regulations.

ABO blood group determination was performed using the Bio-Rad ID-Card gel card system, employing column agglutination technology that integrates antibody-mediated red cell binding with gel filtration [9]. This method ensures high accuracy in routine ABO and RhD typing.

Thrombin generation assays were conducted on the Ceveron® t100 analyzer using the Technothrombin® TGA kit (Technoclone GmbH, Austria). This CE-marked fluorometric assay records continuous thrombin activity over 60 minutes in platelet-poor plasma, initiated with tissue factor, phospholipids, calcium chloride, and a fluorogenic substrate [10]. Key parameters - lag time (LT), peak thrombin (PT), and total thrombin (ttAUC) - were automatically calculated by the system.

Statistical evaluation encompassed descriptive statistics and group comparisons via one-way ANOVA for ABO subgroups and pooled O vs. non-O groups. Correlation analysis between blood group and TGA parameters was performed using Spearman's rank correlation coefficient. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 1,423 patients were included in the analysis (mean age 42 ± 16 years; range 18 - 98), of whom 1,187 were women (83.4%) and 236 were men (16.6%). The distribution across ABO blood groups was: group A (n = 599), group B (n = 233), group O (n = 504), and group AB (n = 84). The mean age was comparable across all groups (range 42 - 43 years; SD ± 16). No significant differences in age or gender distribution were observed between groups (one-way ANOVA, $p > 0.05$). However, men were significantly underrepresented overall ($p < 0.001$) (Table 1).

Thrombin generation by ABO group

Mean lag time differed slightly across groups (Table 2): group B (n = 231) showed the highest value with 4.08 ± 3.11 minutes, followed by group O (n = 504) with 3.81 ± 1.89 minutes, group A (n = 599) with 3.72 ± 1.30 minutes, and group AB (n = 84) with the lowest lag time of 3.62 ± 1.02 minutes. These differences were statistically significant (one-way ANOVA, $F = 5.092$, $p = 0.00165$). However, post-hoc comparisons showed only marginal separation between B/O and AB.

Peak thrombin values ranged from 225.24 ± 120.35 nM in group O to 242.06 ± 123.31 nM in group A, with intermediate values in B (229.35 ± 125.16 nM) and AB (231.00 ± 119.16 nM). These differences were not statistically significant (ANOVA, $F = 0.817$, $p = 0.484$). Total thrombin (area under the curve) ranged from 2,667.14 ± 665.98 nM in group B to 2,784.63 ± 527.79 nM in group A (AB: 2,734.55 ± 488.00 nM; O: 2,693.26 ± 518.51 nM). No statistically significant differences were found across groups (ANOVA, $F = 1.397$, $p = 0.242$) (Table 2).

Comparison between group O and non-O

To further assess the impact of ABO group on thrombin generation, patients were categorized into group O (n = 504) and non-O (groups A, B, AB; n = 912). Lag time was slightly higher in group O (3.81 ± 1.89 minutes) than in non-O (3.80 ± 1.92 minutes), with the difference reaching statistical significance ($p = 0.0149$), albeit clinically irrelevant given the absolute difference of 0.01 minute.

Peak thrombin was lower in group O (225.24 ± 120.35 nM) than in non-O (237.84 ± 123.55 nM), though this difference was not statistically significant ($p = 0.197$).

Table 1. Statistical characteristics of patient groups (* non-O group includes individuals with blood groups A, B, and AB).

	All	A	B	O	AB	Non-O *
N	1.423	599	233	504	84	913
Mean age ± SD, range (years)	42 ± 16 (18 - 98)	43 ± 16 (18 - 87)	42 ± 16 (18 - 87)	43 ± 16 (18 - 89)	42 ± 16 (18 - 84)	43 ± 16 (18 - 87)
Women/men	1,187/236	496/104	193/39	429/76	69/17	758/157

Table 2. Means and standard deviations for lag times (minutes), peak thrombin (nM), and total thrombin (nM) in patient groups with blood groups A, B, O, and AB.

	A	B	O	AB
N	599	231	504	84
Lag time ± SD (range)	3.72 ± 1.3	4.08 ± 3.11	3.81 ± 1.89	3.62 ± 1.02
Peak thrombin ± SD (range)	242.06 ± 123.31	229.35 ± 125.16	225.24 ± 120.35	231.00 ± 119.16
Total thrombin time ± SD (range)	2,784.63 ± 527.79	2,667.14 ± 665.98	2,693.26 ± 518.51	2,734.55 ± 488.00

Table 3. Means and standard deviations for lag times (minutes), peak thrombin (nM) and total thrombin (nM) in patient groups with blood group O and non-O blood groups.

	O	Non-O
N	504	912
Lag time ± SD	3.81 ± 1.89	3.8 ± 1.92
Peak thrombin ± SD	225.24 ± 120.35	237.84 ± 123.55
Total thrombin time ± SD	2,693.26 ± 518.51	2,750.41 ± 564.87

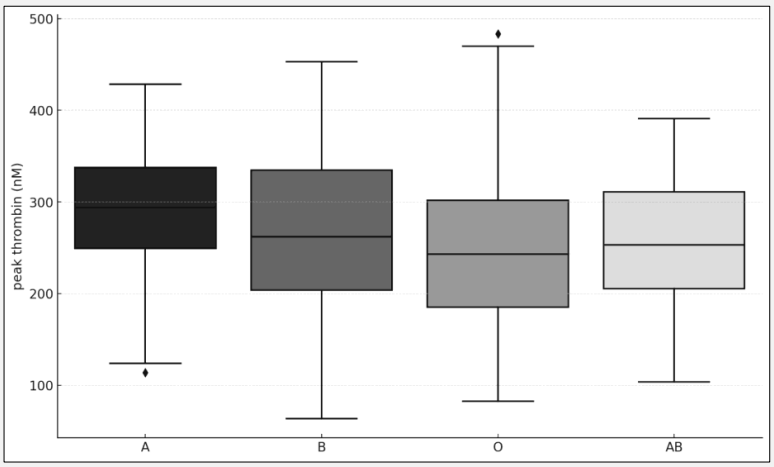

Figure 1. TGA lag times (minutes) in carriers of blood groups A, B, O, and AB.

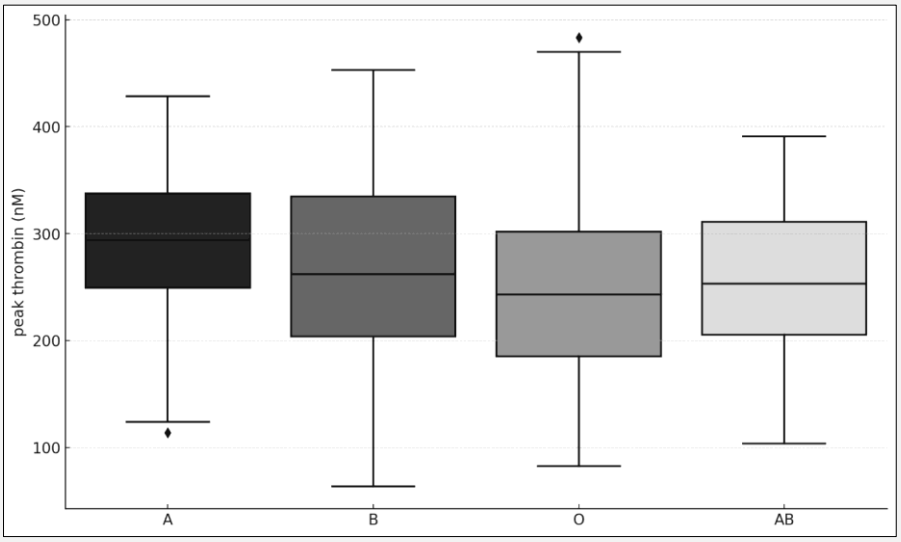

Figure 2. TGA peak thrombin (nM) in carriers of blood groups A, B, O, and AB.

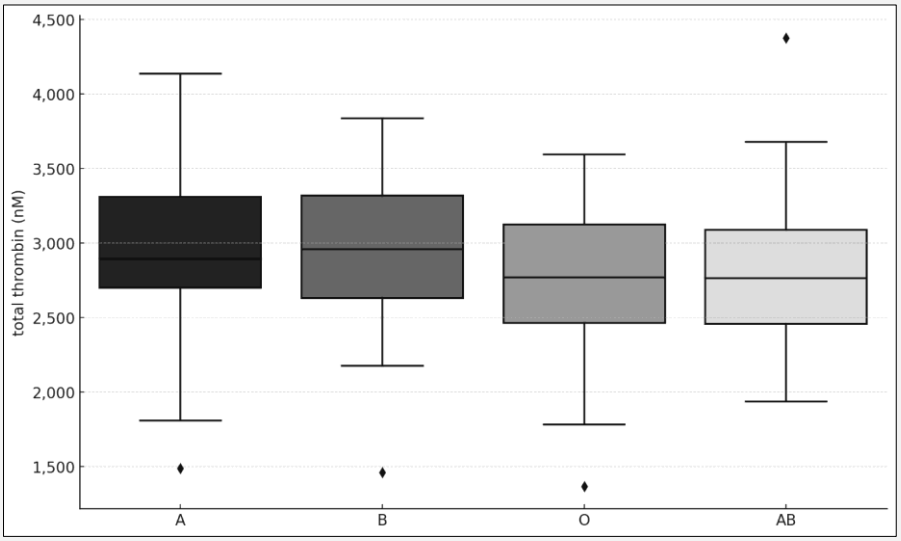

Figure 3. TGA total thrombin (nM) in carriers of blood groups A, B, O, and AB.

Total thrombin was slightly lower in group O (2,693.26 ± 518.51 nM) compared to non-O (2,750.41 ± 564.87 nM), and this difference was statistically significant ($p = 0.0233$). However, the absolute difference of 57.15 nM suggests limited clinical relevance (Table 3).

DISCUSSION

ABO blood groups have long been recognized as modifiers of hemostatic risk. Individuals with blood group O consistently exhibit lower plasma levels of von Wille-

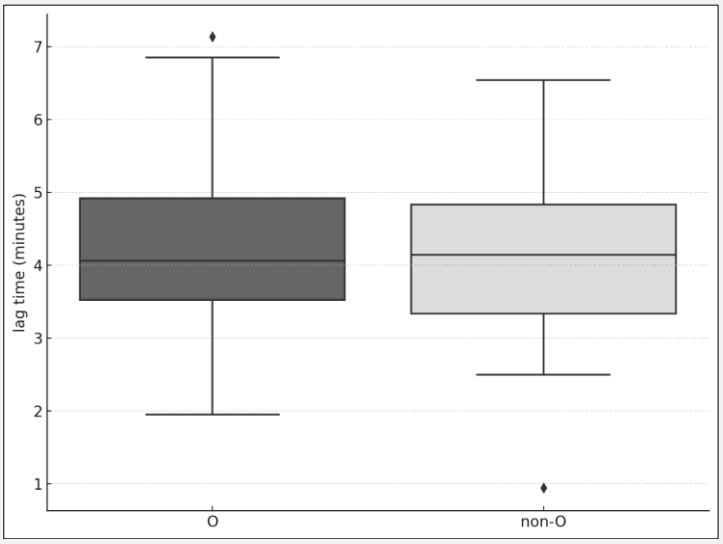

Figure 4. Lag times (minutes) of TGA in carriers of blood group O and carriers of non-O blood groups.

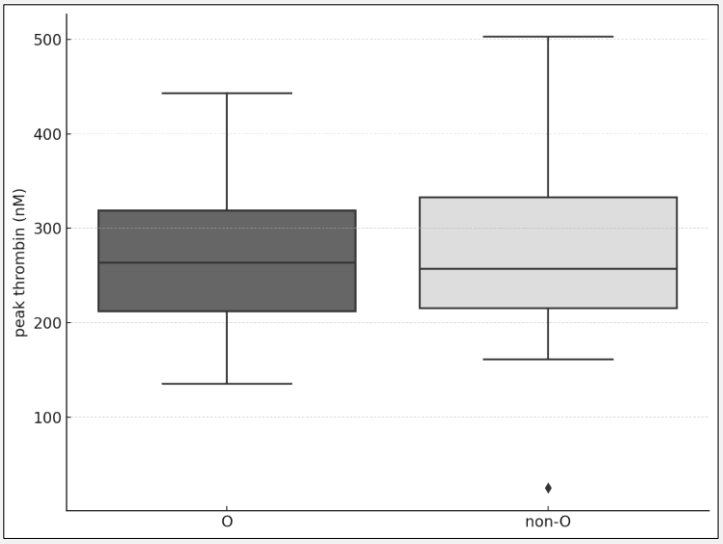

Figure 5. Peak thrombin (nM) of TGA in carriers of blood group O and carriers of non-O blood groups.

brand factor (vWF) and factor VIII (FVIII), which are linked to an increased bleeding tendency [2,11]. In contrast, non-O groups - namely A, B, and AB - are associated with higher levels of these factors and an elevated risk of thrombotic events [5]. These clinical associations have raised the question whether ABO blood group also affects thrombin generation as a mechanistic explanation for such risks [8].

Our present analysis did not confirm a clinically relevant influence of ABO blood group on thrombin gener-

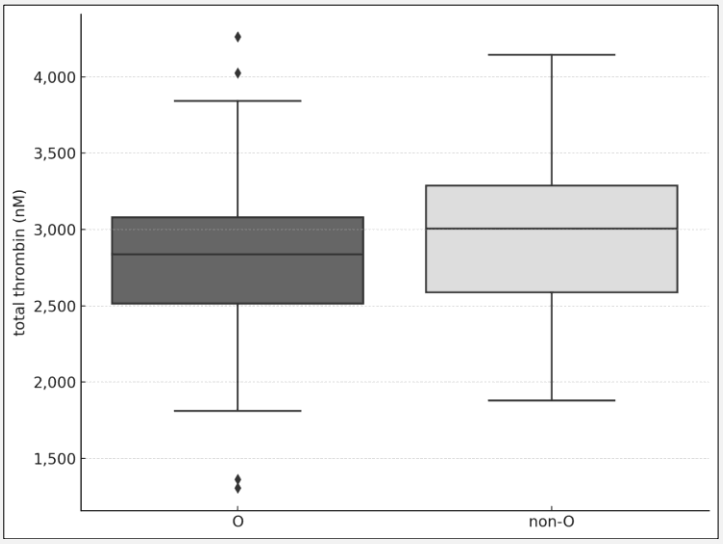

Figure 6. Total thrombin (nM) of TGA in carriers of blood group O and carriers of non-O blood groups.

ation as measured in platelet-poor plasma. Although statistically significant differences were observed for lag time and total thrombin between group O and non-O individuals, these differences were marginal in absolute terms and likely not of physiological relevance. Peak thrombin values showed no significant variation between groups.

These findings are consistent with prior data from Kremers et al., who demonstrated that although ABO group strongly modulates vWF and FVIII levels, it does not significantly affect thrombin generation [8]. One plausible explanation is that vWF is primarily involved in platelet adhesion and not in plasma-based thrombin generation. FVIII may play a more complex role, but its influence on global thrombin formation *in vitro* appears to be attenuated by counterregulatory mechanisms.

Other studies, including Binder et al. [10], have reported modest differences in thrombin generation between ABO types, especially under conditions including platelets or whole blood. Our results confirm that such effects are not evident in platelet-poor systems and suggest that ABO-related thrombotic or bleeding risks are mediated through platelet-dependent or endothelial pathways.

Furthermore, data from large cohort studies have demonstrated that the majority of the ABO effect on thrombosis risk can be attributed to vWF levels [12]. The direct impact of ABO on FVIII, once adjusted for vWF, is minimal. Hence, it is reasonable to conclude that the hemostatic phenotype in ABO groups arises from primary hemostasis and vascular biology rather than intrinsic thrombin generation potential.

CONCLUSION

The absence of clinically meaningful differences in thrombin generation among ABO blood groups supports the hypothesis that variations in bleeding and thrombotic risk are mediated by factors outside the plasma coagulation cascade, such as vWF levels, platelet function, or endothelial interactions. Our findings underline the importance of examining cell-based coagulation models and vessel-wall interactions in future studies.

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Declaration of Interest:
The authors declare that they have no conflicts of interest related to this work.

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