Comparison of Fibrinogen Concentrations Determined by the Clauss Method with Prothrombin-Derived Measurements on an Automated Coagulometer

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Background: This research aims to compare fibrinogen results, obtained from the Clauss and PT-derived method on the Cobas t511 analyzer, in patients with specific categories of disease. A second aim was to determine the reference range for these 2 methods.

Methods: We retrospectively compared fibrinogen concentrations of 914 patients obtained by the Clauss and PT-derived methods on the Cobas t511 coagulation analyzer from the laboratory information system. Fibrinogen data was segregated into a healthy outpatient population and those populations with possible fibrinogen abnormalities including pregnancy, chronic illness, liver disease, heart and vascular diseases, and clinical suspicion of COVID-19. All data were analyzed using Passing–Bablok regression and Bland–Altman analysis. Reference ranges were determined from fibrinogen results of the healthy outpatient population who presented for a clinic check-up.

Results: All fibrinogen results were grouped and compared according to fibrinogen values (low, normal, and high), international normalized ratio (INR) values (<1.2, 1.2–2.0, and >2.0), and diagnosis. There were statistically significant positive correlations in all groups ($P < 0.05$), except for low fibrinogen values ($P = 0.96$). Results with INR value <1.2 had the highest correlation between 2 methods.

Conclusion: The PT-derived method can be used alone in the Cobas t511 analyzer, especially in patients with an INR <1.2. Reported new reference ranges of the PT-derived method could help to determine and compare the clinical significance of fibrinogen methods. Further studies must be focused on the conditions in which PT-derived fibrinogen results should be directed to the Clauss test.

INTRODUCTION

Fibrinogen is an important protein found in plasma and synthesized by the liver. It plays a key role in hemostasis and clot formation (1). Fibrinogen is also a classical positive acute-phase reactant protein elevated in response to inflammation and tissue injury (2). The normal concentration of clottable fibrinogen is approximately 150–400 mg/dL, with significant potential to be affected by many clinical conditions. Low fibrinogen concentrations may be associated with congenital disorders (3), liver disease (4),

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IMPACT STATEMENT

Fibrinogen values obtained from the PT-derived method demonstrate better agreement with the Clauss method in patients with INR levels <1.2.

hemorrhage (5), disseminated intravascular coagulation (DIC) (6), while higher levels may be seen in conditions such as pregnancy (7), inflammation (2), cardiovascular disease (8), and cancer (9). Recently, fibrinogen level evaluation has become even more important with the rise of the coronavirus pandemic. Elevations in fibrinogen may herald the coagulopathy seen in a subset of patients with coronavirus disease-2019 (COVID-19) (10).

The most commonly used method for the determination of fibrinogen concentration is the Clauss method (11). The principle of this method is based on clot formation measured by mechanical or photo-optical means. Plasma is exposed to a reagent containing supraphysiologic concentrations of thrombin, and the time to clot detection is compared to a standard curve constructed with reference plasma (12). The PT-derived fibrinogen test is an alternative method that directly measures fibrinogen using changes in optical densities during the prothrombin time (PT) test. In particular, results derived from PT are considered to have the potential to falsely report fibrinogen concentration as normal in patients with low fibrinogen and a bleeding tendency (13). However, most of the method comparison studies were conducted in small groups of dysfibrinogenemic patients (14). We believe that studies on the effectiveness of the PT-derived method should be elaborated on since no extra reagent is required. Therefore, we aimed to compare Clauss and PT-derived fibrinogen results under different clinical conditions that may affect the fibrinogen level. A recent study suggested that determining fibrinogen reference intervals for both the PT-derived and Clauss methods is important and necessary in comparing the 2 methods (15). The second aim of the present study was to determine the reference range for the 2 methods.

MATERIALS AND METHODS

This study was performed in the clinical chemistry laboratory of Zonguldak Bülent Ecevit University Hospital in 2020. Data were collected retrospectively from 914 participants who had their PT and fibrinogen levels assessed. The study protocol was approved by the Ethics Committee of Zonguldak Bülent Ecevit University and performed according to the principles of the Declaration of Helsinki.

Analysis of Blood Samples

Venous blood samples taken into 2-mL tubes with 0.109 mol/L sodium citrate system for anticoagulation were centrifuged at 2000*g* for 15 min for plasma separation and then analyzed immediately. Samples were analyzed using fibrinogen (Clauss method) and PT (thromboplastin) kits in a Cobas t511 (Roche Diagnostics GmbH) coagulation analyzer. The measuring principle of Clauss and the PT-derived method is based on clot formation. The Clauss method measures fibrinogen levels generated in a diluted plasma sample in the presence of excess thrombin. The PT-derived method is based on changes in turbidity that occur during the clot formation triggered by tissue thromboplastin on an automated coagulometer. The measuring range of the Cobas fibrinogen kit using the Clauss method is 0.6–9 g/L and the limit of quantitation was 0.6 g/L. The within- and total-run coefficient of variation values were <2% and <3%, respectively. Expected values in the Cobas

fibrinogen kit using the Clauss method are 1.93–4.12 g/L. All assays were performed according to their respective manufacturers' instructions. The quality control measurements of PT and fibrinogen were performed at least twice every day.

Study Population

The comparison was performed in patient specimens referred to the laboratory for routine coagulation testing. Patients for whom PT and fibrinogen tests were analyzed together were included in the study. In this way, plasma fibrinogen levels were obtained from the PT-derived simultaneously, with the Clauss method being a routine method in our laboratory. We recorded fibrinogen results obtained from 2 methods and international normalized ratio (INR) levels of all results. The population was divided by disease state classifications likely to affect fibrinogen level such as pregnancy, chronic diseases (particularly prominent diabetes mellitus, renal disease, chronic obstructive pulmonary disease, cancer, inflammatory diseases, etc.), liver disease (complicated or noncomplicated with chronic diseases), heart and vascular diseases (complicated or noncomplicated with chronic diseases [hypertension, arrhythmias, coronary heart disease, valvular heart disease, thromboembolic disease, stroke, etc.]), and clinical suspicion of COVID-19. Patients who applied to the pandemic outpatient clinic with the suspicion of COVID-19 were evaluated in the COVID-19 group, although they had other diseases. The diagnosis of COVID-19 was not confirmed because the PCR results of these patients were unavailable. In addition, we composed a healthy population from fibrinogen results of patients who visited an outpatient clinic for mostly check-ups. This population had no acute or chronic infection associated with increased C-reactive protein, no history of venous thrombosis, no anticoagulation, and no history of cardiovascular, lung, autoimmune, cancer, kidney, liver, hematologic, or chronic diseases. Subsequently, the healthy population was grouped by gender and age (ages <18 as pediatric, ages >18 as adult).

Statistical Analysis

The distribution of data was assessed by using Shapiro–Wilk tests. Method comparisons were evaluated using MedCalc Statistical Software (v.12, MedCalcSoftware). The correlation between the 2 methods was calculated using a nonparametric Passing–Bablok regression analysis. The degree of correlation between assays was determined by the nonparametric Spearman rank correlation coefficient. *P* values of <0.05 were considered statistically significant. Bias was examined using Bland–Altman analysis and the mean difference between results was reflected as the systematic bias. Bias >20% was considered to be clinically unacceptable (16).

The nonparametric method was used to calculate the reference interval. Extreme values were excluded using SPSS 16.0 (SPSS). Reference ranges were calculated based on the 2.5th and 97.5th percentile values of the levels in both methods with 90% confidence intervals (CI), as recommended by the IFCC (CLSI C28-A3), and were accompanied by median and mean values.

RESULTS

The data profile formed using fibrinogen results consisted of participants between 1 and 80 years of age: 448 females and 466 males. All results were sorted according to reference ranges of the Clauss method as low, normal, and high fibrinogen levels. In this sorting, 18 patients (2%) had low fibrinogen levels, 697 patients (76%) had normal fibrinogen levels, and 199 patients (22%) had high fibrinogen levels. Also, all results were sorted according to INR levels as <1.2, 1.2–2, and >2.0. Of the 914 results used for this study, 660 (72%) had INR results <1.2, 226 (25%) had INR results between 1.2 and 2.0, and 28 (3%) had INR results >2.0.

We compared PT-derived fibrinogen results with those from the Clauss method in groups of 161 healthy, 20 pregnant women, and 733 patients. The number of patients of each disease subgroup was as follows: liver disease (39, 5%), heart and vascular disease (132, 18%), chronic disease (137, 19%), and suspicion of COVID-19 (425, 58%).

Method Agreement

The Passing–Bablok regression analysis yielded the equation $y = 1.034x + 3.44$ and the Spearman rank correlation coefficient was 0.91 (95% CI, 0.898 and 0.920) for all the results ($P < 0.0001$). The Bland–Altman difference plot showed that the mean bias was 15.3 (4.5%). Regression analyses and Bland–Altman plots between 2 methods for all the results were shown in Figs. 1A and 1B. Figure 2A–E provides box plots for each disease population and test methodology.

Results of the method comparison for the whole group are summarized in Table 1. When comparing PT-derived fibrinogen and Clauss fibrinogen results, a statistically significant correlation was observed in all groups, except for low fibrinogen levels. Bland–Altman analysis assessing the agreement between the PT-derived method and the Clauss method demonstrated that only the bias level in low fibrinogen levels is unacceptable for clinical use.

When the investigation of diagnosis of patients who had low fibrinogen levels, 55% of those patients had heart and vascular disease, 17% had liver disease, 11% had a chronic disease, 11% had COVID-19, and 6% were pregnant.

Reference Ranges

Reference ranges were determined by using the results of the healthy population. The reference intervals for the Clauss fibrinogen and PT-derived fibrinogen are presented in Table 2.

According to manufacturer reference ranges, the patients should be classified as follows: 18 patients had low fibrinogen levels by the Clauss assay, and 3 patients had low fibrinogen levels by the PT-derived method (17%). According to the reference intervals determined in our healthy population, 25 patients had low fibrinogen levels by the Clauss assay, while 19 patients had low fibrinogen levels by the PT-derived assay (76%).

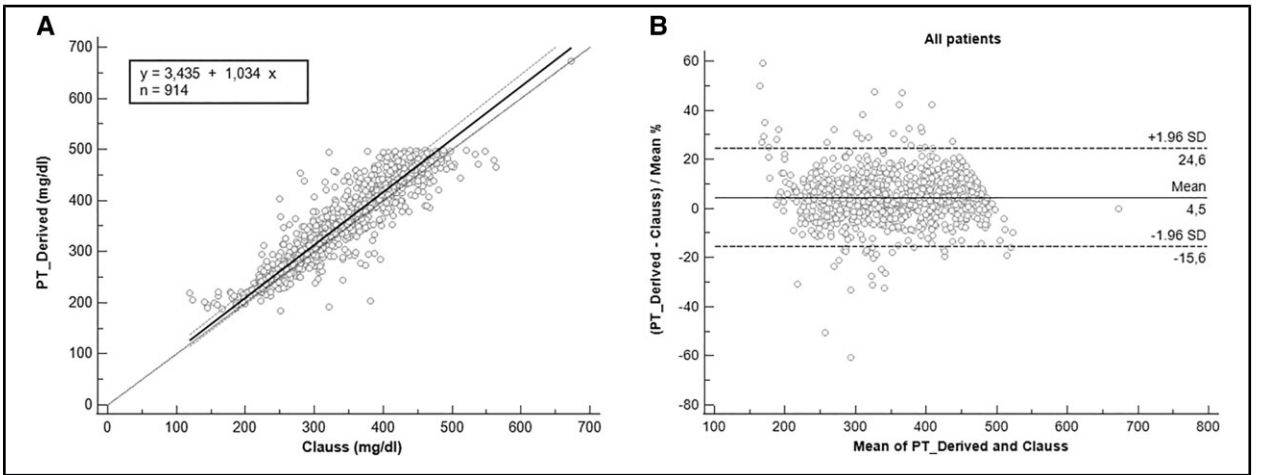

Fig. 1. (A) Passing–Bablok regression analysis and (B) Bland–Altman plot analysis between the Clauss and PT-derived fibrinogen assays for all patients.
(Black solid line: regression line; gray dashed line: 95% CI for the regression line; Black dotted line: line of identity).

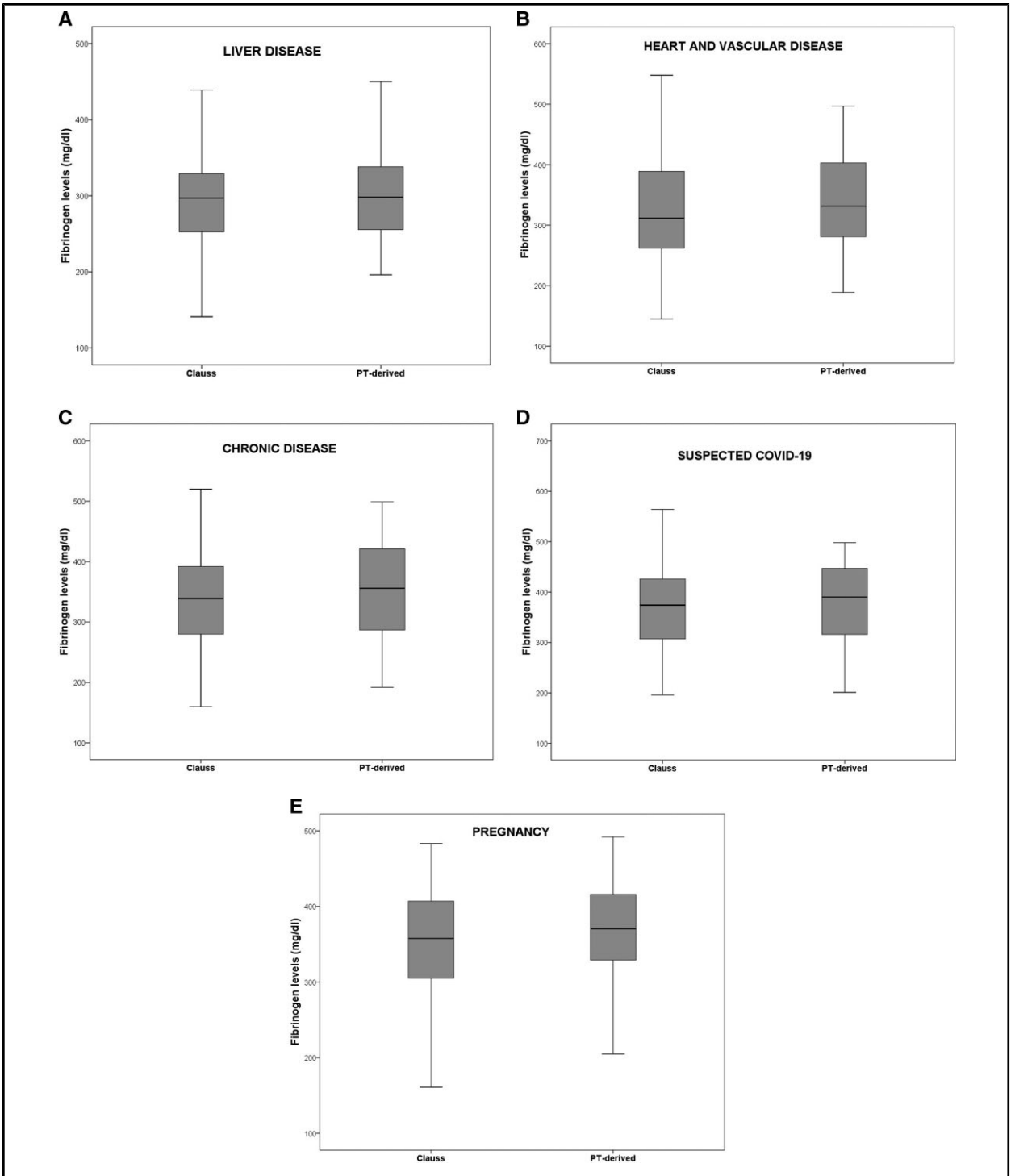

Fig. 2. Box plots comparing fibrinogen measurements for each disease population by the Clauss and PT-derived methods: (A), liver disease; (B), heart and vascular disease; (C), chronic disease; (D), suspected COVID-19; and (E), pregnancy.

Table 1. Results of method comparison for all groups.

		Passing–Bablok regression		Spearman rank		Bland–Altman plot	
Groups	*n*	Intercept (95%CI)	Slope (95%CI)	Coefficient	Significance level	Bias (95%CI)	Bias% (95%CI)
INR <1.2	660	0.86 (−7.84–9.69)	1.03 (1.00–1.05)	0.93	<0.0001	10.6 (−48.5–69.7)	3.0 (−14.4–20.4)
INR 1.2–2.0	226	−1.42 (−20.4–15.7)	1.08 (1.02–1.14)	0.92	<0.0001	23.1 (−50.8–97.0)	6.9 (−15.1–28.9)
INR >2.0	28	−27.85 (−156.5–56.5)	1.33 (0.99–1.77)	0.61	=0.0005	57.4 (−54.8–170)	18.2 (−15.6–51.9)
Low fibrinogen level	18	152.5 (65.7–208.8)	0.31 (−0.04–0.85)	0.01	0.96	41.2 (−7.5–89.9)	23.0 (−6.4–52.4)
Normal fibrinogen level	697	−30.11 (−43.1– −18.6)	1.15 (1.11–1.19)	0.86	<0.0001	17.0 (−51.1–85.2)	4.9 (−15.4–25.1)
High fibrinogen level	199	−88.24 (−212–10.0)	1.22 (1.00–1.50)	0.48	<0.0001	6.8 (−55.7–69.2)	1.5 (−12.3–15.3)
Pregnancy	20	65.42 (−33.7–107)	0.87 (0.74–1.15)	0.88	<0.0001	14.6 (−58.1–87.3)	6.0 (−22.4–34.5)
Liver disease	39	2.62 (−52.3–49.9)	1.02 (0.85–1.20)	0.92	<0.0001	12.7 (−42.0–67.4)	4.6 (−15.4–24.6)
Heart and vascular disease	132	24.48 (5.72–41.57)	0.98 (0.92–1.03)	0.88	<0.0001	16.6 (−59.4–92.7)	5.6 (−18.1–29.3)
Chronic diseases	137	−3.42 (−27.5–19.0)	1.07 (1.00–1.14)	0.88	<0.0001	21.7 (−55.2–98.5)	6.0 (−16.6–28.7)
Suspected COVID–19	435	0.39 (−14.9–13.0)	1.04 (1.00–1.08)	0.89	<0.0001	13.9 (−54.9–82.6)	3.8 (15.5–23.0)

DISCUSSION

This study is important in terms of good agreement of the comparison of fibrinogen levels between the 2 methods performed on the Cobas t511 analyzer ($r = 0.91$). The correlation coefficients were similar to a previous study, in which 2 fibrinogen methods were compared on the Cobas t711 coagulation analyzer using the same kits (17). Results from that study were based on only 120 samples without corresponding INR levels or the patient disease classification. The results of our evaluation demonstrated a slightly better agreement for INR levels <1.2 ($r = 0.93$). In addition, there was a weak positive correlation in results having INR >2 and high fibrinogen levels, but no significant correlation for low fibrinogen levels. INR-related performance reported may be specific for the thromboplastin type used (18). We found that PT-derived values were consistently higher than the Clauss measurements according to Bland–Altman analysis. However, the accuracy assessment between the 2 methods for all the results was 4.5%, which was within the acceptable limits of fibrinogen as defined by the CAP (16).

A multicenter study of 1441 participants is valuable in terms of being an early and large-scale study to compare fibrinogen methods. Similar mean values and distributions in methods from PT-derived and Clauss were shown in a recent investigation, despite the use of different instruments and reagents (19). Although these results were encouraging, the researchers recommended

Table 2. The reference intervals for the Clauss fibrinogen and PT-derived fibrinogen.

		Clauss method fibrinogen level (g/L)			PT-derived fibrinogen level (g/L)		
	n	Mean ± 2SD	Median	2.5%–97.5%	Mean ± 2SD	Median	2.5%–97.5%
Total	161	3.14 ± 0.7	3.05	2.05–4.60	3.27 ± 0.7	3.18	2.19–4.84
Adult women	71	3.19 ± 0.6	3.10	2.07–4.31	3.28 ± 0.7	3.20	2.23–4.47
Adult men	38	3.31 ± 0.7	3.22	2.28–4.69	3.45 ± 0.7	3.44	2.19–4.92
Girls (<18 years)	24	2.86 ± 0.6	2.72	1.96–4.02	3.09 ± 0.7	2.95	1.97–4.40
Boys (<18 years)	28	3.03 ± 0.7	2.90	2.02–4.85	3.21 ± 0.8	3.05	1.87–4.84

further investigations into the causes and clinical significance of discrepancies between the fibrinogen assays in the general population. They had found a lack of agreement in high and low fibrinogen levels, similar to our results. The researchers thought that heterogeneity of plasma fibrinogen may be relevant to ischemic heart disease risk in a large and random sample of the general population. In line with their thoughts, we also observed that the group with low fibrinogen values, in which there was little agreement between the 2 methods, mainly consisted of patients with cardiovascular diseases. The potential for anticoagulant use in cardiovascular patients could contribute to relatively low Clauss values and higher PT-derived fibrinogen values in our study. Anticoagulant agents, especially new-generation anticoagulants such as direct thrombin inhibitors, may inhibit the thrombin contained in the Clauss reagent. Thus, they may prolong time to clot formation and underestimate the fibrinogen concentration (20, 21). Also, the concentration of thrombin in the Clauss reagent can vary by manufacturer and instrumentation (13). Therefore, instead of the Clauss assay method, the PT-derived method may be more valuable in seeing fibrinogen's contribution to the clot. It should be noted that the Clauss method is not the gold standard in many cases due to its high heparin level and potential to be affected by fibrin degradation products (13). Recently, there have been many reports that new methods such as the fibrin-based thromboelastometry method and dry hematology method should be used instead of Clauss and PT-derived methods in patients whose fibrinogen level is closely monitored for fibrinogen supplementation (22, 23).

We believe that the PT-derived method should be strongly considered for laboratory test menus. This method is important in terms of cost and waste minimization, as it provides fibrinogen results without the need for extra reagent in patients where PT and fibrinogen results are required together (15). Also, for the fibrinogen test, the turnaround time of the Clauss method is longer than the PT-derived method. The result of the fibrinogen test can be added to the PT test as a subtest so that it can be used, whether as a cost-effective subtest or a quick result for the clinician. However, overestimating the PT-derived method in patients with low fibrinogen may be a clinical problem. When focusing on the clinical significance of differences between the 2 assays, several studies reported that the PT-derived method is not reliable in some clinical settings, particularly in patients with dysfibrinogenemia (14, 24, 25). The most important advantage of our study is that it demonstrates fibrinogen differences between disease states in a large population. Nevertheless, it has some limitations. The main limitation of this study is that the diseases with which the study participants are matched are classified roughly. Therefore, we do not have information about

whether there are dysfibrinogenemic patients in our study groups. Another limitation of the study was lack of access to medication lists for the studied population, and therefore, the inability to screen for those medications that may affect fibrinogen levels.

The present study demonstrated that the reference interval of the PT-derived method tended to be higher than for the Clauss assay. For this reason, it does not seem appropriate to evaluate the results of the PT-derived method with reference intervals performing by the Clauss assay, especially in low fibrinogen levels. We also observed lower fibrinogen in women or younger age groups than in men or adult age groups for both the Clauss and PT-derived method. Hence, it is necessary to establish of gender- and age-specific fibrinogen reference ranges for the 2 methods.

In conclusion, the PT-derived method is not interchangeable with Clauss assays in patients with low fibrinogen. The Clauss assay is not ideal for plasma fibrinogen monitoring in most patients with a high risk of bleeding. Therefore, we think that the PT-derived method can be used alone on the Cobas t511 analyzer, especially in patients with an INR <1.2. Reported new reference ranges of PT-derived method could help to determine and compare the clinical significance of fibrinogen methods. Further studies must be focused on the conditions in which PT-derived fibrinogen results should be directed to the Clauss test.

Nonstandard Abbreviations: INR, international normalized ratio; PT, Prothrombin time; INR, international normalized rate; COVID-19, coronavirus disease 2019; CAP, College of American Pathologists.

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B. Guven researched literature and conceived the study. B. Guven, M. Can, and A. Tekin were involved in gaining ethical approval, collection, and analysis of data. B. Guven wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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