Establishment of normal reference range for thromboelastography based on 17,708 cases in Beijing, China

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Background: Thromboelastography (TEG) can dynamically evaluate the interaction between platelets and coagulation cascade and the effects of other cellular components on the activities of plasma factors, to comprehensively analyze the whole process of blood coagulation and dissolution. Due to differences in both the incidence rates and the coagulation state of related diseases, many studies have highlighted the necessity of establishing the normal reference ranges for TEG for local regions. The aim of the present study was to determine the local normal reference ranges according to the TEG results of 17,708 volunteers in Beijing, to explore the coagulation characteristics related to the age and sex of the study population.

Methods: Reference ranges of reaction time (R), coagulation time (K), coagulation angle (α-angle), and maximum thrombus consistency (MA) for TEG in healthy adults in Beijing were determined in the physical examination of 17,708 Beijing volunteers (5,319 women and 12,389 men). The volunteers were divided into the elderly group (≥60 years old) and young and middle-aged group (20–59 years old), and the reference ranges of each group were calculated according to sex.

Results: Based on the TEG results of the 17,708 volunteers who underwent physical examination, the 95% reference ranges of R, K, α-angle, and MA for TEG in Beijing were 5.1–10 min, 1.3–3.8 min, 44.9–70.2°, and 50.4–71 min, respectively. The results of R, K, α-angle, and MA for TEG between the young and middle-aged group and the elderly group, as well as between women and men were significantly different ($P<0.001$). Finally, reference ranges for TEG in the young and middle-aged group and the elderly group were obtained.

Conclusions: Compared with the reference standards provided by previous reagent manufacturers, the coagulation factor and fibrinogen function of TEG tend to be hypocoagulable in Beijing population. We found that the young and middle-aged group had lower coagulation activity than the elderly group, and women had higher coagulation activity than men in the same group.

Keywords: Thromboelastography (TEG); elderly people; sex; reference range

Submitted Feb 28, 2022. Accepted for publication May 10, 2022.
doi: 10.21037/atm-22-1731
View this article at: https://dx.doi.org/10.21037/atm-22-1731

Introduction

Thromboelastography (TEG) was first developed by Dr. Hellmut Hartert from Heidelberg University (Germany) in 1948 (1). It was originally used to monitor the changes in coagulation and fibrinolysis associated with liver transplantation. In recent years, TEG has been widely used in cardiovascular diseases, and its role in improving the results of cardiac surgery has been affirmed (2). Randomized controlled trials have shown that TEG can reduce blood transfusion and reoperation due to postoperative bleeding in patients undergoing cardiac surgery, and reduce overall mortality (2,3).

There are many coagulation activity tests at present, such as prothrombin time, international normalized ratio, activated partial thromboplastin time, platelet count, fibrinogen concentration, D-dimer level, activated clotting time, and bleeding time. However, these tests cannot provide a complete coagulation state, because it is impossible to evaluate some coagulation factors, platelet function, and the activity of the fibrinolytic system based on these. By tracking the dynamic coagulation process curve with TEG, we can dynamically analyze the interaction between blood components, such as platelets, coagulation factors, and fibrinogen, as well as the whole process of thrombosis and fibrinolysis (4). In addition, TEG is significant in determining the cause of bleeding, evaluating perioperative risk, and monitoring the effect of anticoagulants (5).

At present, there is no standard TEG reference range provided by China. The reference ranges for TEG that are currently used in China are based on those in the manufacturer's manual, which is mainly based on the Western population. Its main disadvantage is that it does not provide information on the repeatability and variability of the measurement, and the impact of the age, sex, and race of target people on the results. Due to the mismatch between the manufacturer's reference ranges and target population, healthy people of different races or from different regions could be classified as hypocoagulable/hypercoagulable. At present, it is believed that the main reason for the different reference ranges of TEG is the difference of coagulation state *in vivo* caused by ethnic and regional differences, therefore, some countries have established their own reference ranges of healthy people (6,7). In 2011, Ji *et al.* published a reference standard for TEG in Beijing based on the test results of 137 volunteers (8). Different from their study, our study included a total of 17,708 volunteers from 169 units and individuals in Beijing with an age range of 20–95, aiming to determine the local normal reference ranges according to the TEG results of 17,708 volunteers in Beijing, who underwent a physical examination, to explore the coagulation characteristics related to the age and sex of the study population. We present the following article in accordance with the MDAR reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1731/rc).

Methods

Study participants

A total of 17,708 volunteers (5,319 women and 12,389 men) from 169 companies and families in Beijing were examined in the Physical Examination Center of Electric Power Teaching Hospital from January 2020 to December 2021. The volunteers' ages ranged from 20 to 95 years. Women volunteers were not menstruating on the day of blood drawing, and all volunteers fasted before blood drawing. The volunteers had no symptoms, such as fever and cough within 14 days, and had not been to COVID-19 risk areas.

Experimental methods

A total of 3 mL of venous blood was collected, placed into a vacuum tube with 3.2% sodium citrate additive (Greiner Bio-One, Beijing, China), mixed, and then left to sit at room temperature. Detection was completed within 4 h after blood collection. First, a TEG-matched activated coagulation reagent bottle (Chongqing DingRun, Chongqing, China) was placed at room temperature for 30 min. The vacuum tube was turned upside down 5 times to mix it well. Take 1 mL blood from the vacuum tube and add it into the activated coagulation reagent bottle (Chongqing DingRun, Chongqing, China), and turn the bottle upside down for 5 times to mix it well. The sample cup (Chongqing DingRun, Chongqing, China) was fixed to the thromboelastogram analyzer (DRNX-III, Chongqing DingRun, Chongqing, China), and 20 μL calcium chloride was added into the sample cup. Take 340 μL well-mixed blood from the activated coagulation reagent bottle and add it into the cup and start testing. The test was performed at a constant temperature of 37 ℃. The measured parameters included reaction time (R), coagulation time (K), coagulation angle (α-angle), and maximum thrombus consistency (MA). LY30 and Coagulation index (CI) are fibrinolysis related test indexes, and no abnormal fibrinolysis volunteers were found in this study. Therefore, these two indexes were not included in the study.

Statistical analysis

SPSS version 26.0 (IBM, Armonk, NY, USA) was used for the statistical analysis. Based on the current reference standards for R, K, α-angle, and Ma, the proportion of abnormal values detected by TEG in the 17,708 volunteers was calculated and expressed as n (%). Based on this, 95%

reference ranges were used as the reference standards of the Beijing population. The volunteers were divided into the following two groups according to age: the young and middle-aged group (20–59 years, with an average age of 44 years) and the elderly group (≥60 years, with an average age of 68 years). Variance analysis was used to compare the differences in R, K, α-angle, and Ma between groups and sexes. P values were <0.001 in all comparisons, and the differences were statistically significant. TEG reference ranges among men and women in each group were formulated with 95% reference ranges.

Ethical statement

The present study was approved by the Ethics Committee of Electric Power Teaching Hospital (No. 2022-ky-03-01) and does not involve confidential content. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent from participants for this retrospective analysis was waived.

Results

Normality of the results of R, K, α-angle, and MA for TEG of the 17,708 volunteers who underwent physical examination in Beijing was tested. The results were all found to be normally distributed. The probability-probability plot of the normality test of R, K, α-angle, and MA is shown in *Figure 1*.

Based on the results of TEG in the 17,708 volunteers, we found that the results of 1,554 people exceeded the reference standard of the R (4–9 min), and abnormal values accounted for 8.8%. The results of 1,972 people exceeded the reference standard of the K (1–3 min), and abnormal values accounted for 11.1%. The results of 3,462 people exceeded the reference standard of α-angle (53–72º), and abnormal values accounted for 19.6%. The results of 989 people exceeded the reference standard of MA (50–70 min), and abnormal values accounted for 5.6% (*Table 1*). Taking the reference standards provided by previous reagent manufacturers as the benchmark, the TEG results of people in Beijing tended to have a high abnormal rate. Therefore, we obtained the 95% reference ranges for TEG of healthy adults in Beijing after the calculation of the TEG results of 17,708 volunteers in Beijing who underwent physical examination. These were as follows: R: 5.1–10 min, K: 1.3–3.8 min, α-angle value: 44.9–70.2°, and MA: 50.4–71 min (*Table 2*).

Comparison between men and women in the study cohort showed that the R of women (mean: 6.943 min) was lower than that of men (mean: 7.315 min), the K of women (mean: 1.927 min) was lower than that of men (mean: 2.402 min), the α-angle of women (mean: 62.739º) was higher than that of men (mean: 57.367º), and the MA of women (mean: 63.612 min) was higher than that of men (mean: 60.392 min). The differences were statistically significant (P<0.001). A scatterplot of the changes of R, K, α-angle, and MA of TEG with age is shown in *Figure 2*. Compared with the elderly group, the young and middle-aged group had a higher R (mean: 7.262 min *vs.* mean: 6.996 min), a higher K (mean: 2.242 min *vs.* mean: 2.087 min), a lower α-angle value (mean: 59.14º *vs.* mean: 60.967º), and a lower MA (mean: 61.434 min *vs.* mean: 62.570 min). The differences were statistically significant (P<0.001) (*Tables 3-5*).

After carefully considering the influence of age and sex on TEG results, we proposed reference ranges of healthy adults of different ages and sexes in Beijing, as shown in *Table 6*. In the young and middle-aged group, the reference range of the R was 5.2–10.2 and 5.0–9.5 min for men and women, respectively; the reference range of the K was 1.5–3.8 and 1.2–3.1 min for men and women, respectively; the reference range of the α-angle was 43.8–67.6º and 50.7–71.4º for men and women, respectively; and the reference range of the MA was 50.0–69.2 and 51.5–72.1 min for men and women, respectively. In the elderly group, the reference range of the R was 4.8–9.9 and 4.9–9.4 min for men and women, respectively; the reference range of the K was 1.2–3.9 and 1.2–2.9 min for men and women, respectively; the reference range of the α-angle was 44.0–71.0º and 52.4-73º for men and women, respectively; and the reference range of the MA was 49.8–71.3 and 52.9–73.5 min for men and women, respectively.

Discussion

Coagulation is an inherent property of the blood system. In the healthy state, normal blood flow is maintained by the balance between procoagulant substances and anticoagulant factors. The normal response of the body to bleeding is the formation of stable blood clots in the process of bleeding, which is called coagulation. Hypercoagulable state and thromboembolism are the result of hyperactivity of coagulation-promoting factors or lack of anticoagulants. Arterial thrombosis is mainly caused by the rupture of atherosclerotic plaque, around

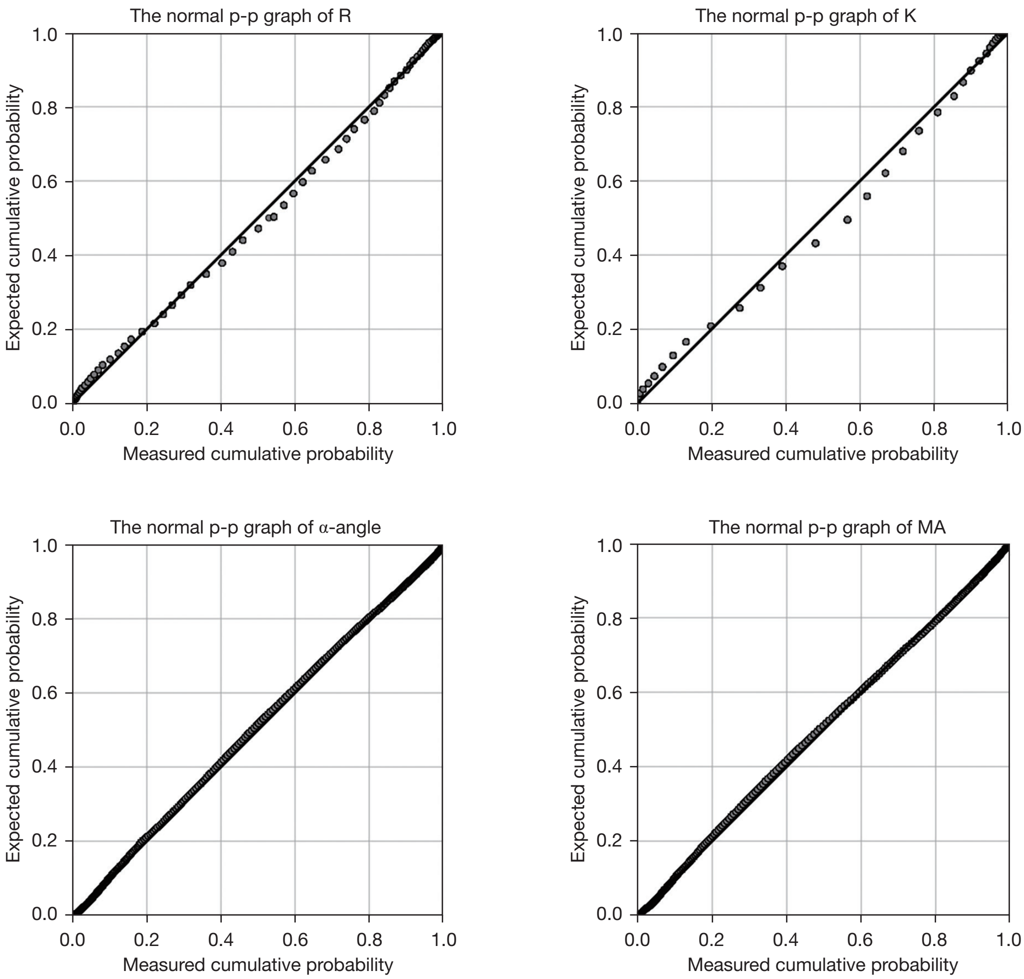

Figure 1 Probability-probability graphs of R, K, α-angle, and MA for TEG in the 17,708 participants who underwent physical examination. R, ranges of reaction time; K, coagulation time; α-angle, coagulation angle; MA, maximum thrombus consistency; TEG, thromboelastography.

Table 1 Proportion of abnormal results among the 17,708 participants who underwent physical examination

Variables (currently used reference range)	Below currently used reference range (%)	Above currently used reference range (%)	Total (%)
R (4–9 min)	51 (0.3)	1,503 (8.5)	1,554 (8.8)
K (1–3 min)	33 (0.2)	1,939 (10.9)	1,972 (11.1)
α-angle (53–72°)	3,273 (18.5)	189 (1.1)	3,462 (19.6)
MA (50–70 min)	342 (1.9)	647 (3.7)	989 (5.6)

R, ranges of reaction time; K, coagulation time; α-angle, coagulation angle; MA, maximum thrombus consistency.

Table 2 Results of the 17,708 participants who underwent physical examination

Parameters	R (min)	K (min)	α-angle (°)	MA (min)
Mean ± SD	7.29±1.26	2.3±0.62	58.4±6.5	61.1±5.2
Our 95% reference range	5.1–10.0	1.3–3.8	44.9–70.2	50.4–71.0
Currently used reference range	4–9	1–3	53–72	50–70

R, ranges of reaction time; K, coagulation time; α-angle, coagulation angle; MA, maximum thrombus consistency; SD, standard deviation.

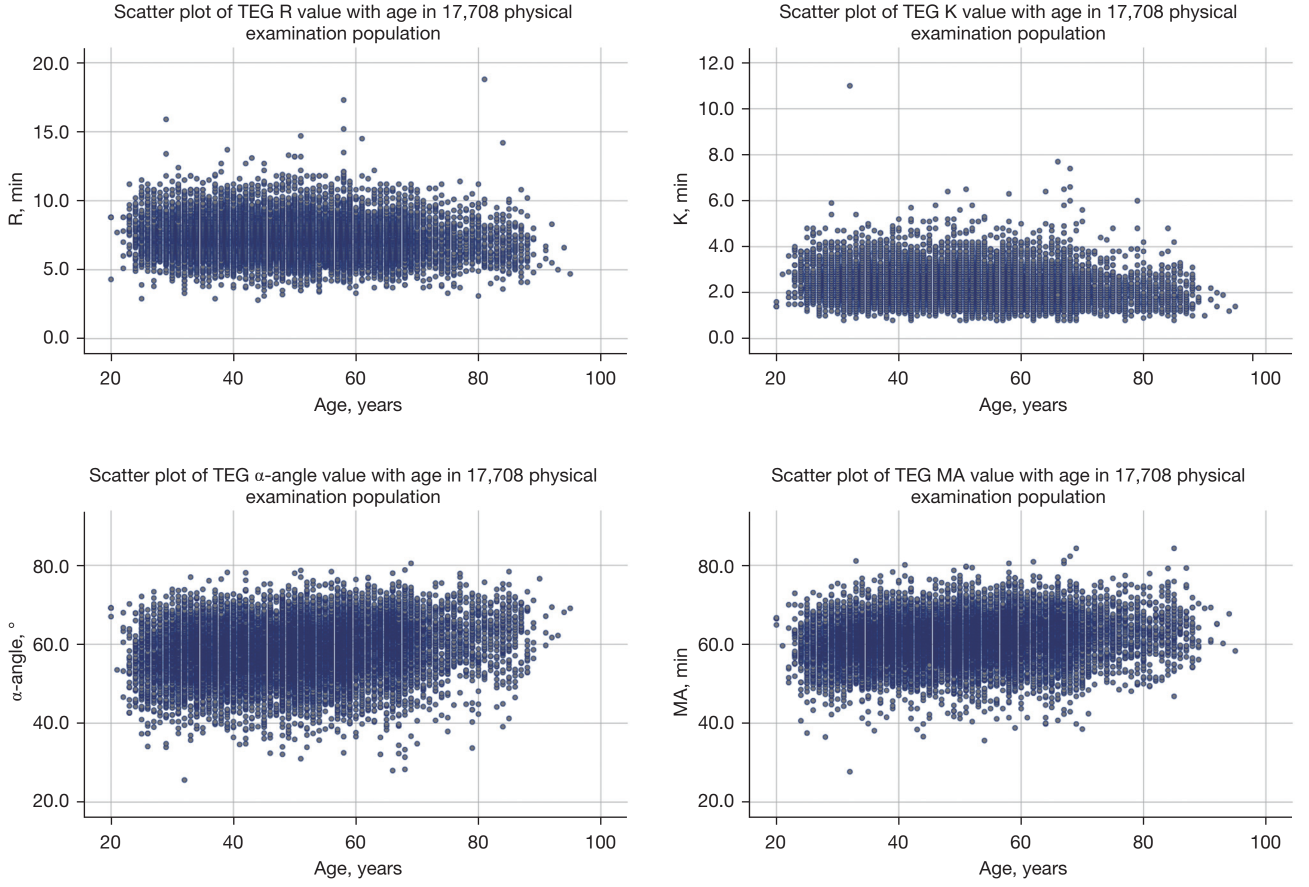

Figure 2 Scatter plot of the changes in R, K, α-angle, and MA for TEG based on age in the 17,708 participants who underwent physical examination. R, ranges of reaction time; K, coagulation time; α-angle, coagulation angle; MA, maximum thrombus consistency; TEG, thromboelastography.

Table 3 Sex distribution of the study cohort

Sex	n [%]
Women	5,319 [30]
Men	12,389 [70]

which white thrombi rich in platelets are formed, resulting in myocardial infarction, stroke, and other diseases. Stasis behind the venous valve leads to venous thrombosis and red thrombosis, mainly resulting in deep venous thrombosis and pulmonary embolism (9). A thromboelastogram analyzer that dynamically detects the whole process of coagulation from the aspects of coagulation, platelet aggregation, and fibrinolysis. It can dynamically evaluate the interaction between platelets and coagulation cascade and the influence of other cell components (e.g., leukocytes and erythrocytes) on the activity of plasma factors, to comprehensively analyze the whole process of blood coagulation and dissolution. TEG is a reliable and sensitive method to judge the state of coagulation. At present, it has a wide range of applications, including in cardiovascular disease, surgery, guidance for anticoagulant administration, and blood transfusion. However, since the application of TEG in China in 2006, reference ranges based on the population of Western countries have been used. There is evidence that different incidences of related diseases and different coagulation statuses in different ethnic groups and regions will lead to differences in normal reference ranges of TEG results (10-16). In recent years, many studies have highlighted the importance of establishing normal reference ranges for TEG for local regions (6,17,18). Ni *et al.* and Ji *et al.* reported their research results based on the Weihai population and Beijing population China, respectively (5,8). However, such studies are mostly limited to small sample studies or inpatients. Unlike previous studies, our study overcame the limitations of small samples and included 17,708 volunteers who underwent routine physical examination in Beijing. We found that nearly 20% of the cohort (3,462 people) had abnormal results based on previous reference standards. These results were similar to those of Scarpelini *et al.* (6). We obtained 95% reference ranges for the Beijing population based on the following results: R: 5.1–10 min, K: 1.3–3.8 min, α-angle: 44.9–70.2°, and MA: 50.4–71 min. Compared with the Western population, the results of our study showed that healthy adults in Beijing had a longer coagulation reaction time, suggesting that the level of coagulation factors was lower and coagulation time was prolonged, indicating lower fibrinogen function. Our cohort also had a slightly higher

Table 4 Age distribution of the study cohort

Parameters	Young and middle-aged group (20–59 years)	Elderly group (≥60 years)
n (%)	13,901 (78.5)	3,807 (21.5)
Mean ± standard deviation	44±9.5	68±6.8
Minimum–maximum	20–59	60–95

Table 5 Effect of sex and age on thromboelastography results

Variables	Sex			Age (years)		
	Women	Men	P value*	Young and middle-aged group	Elderly group	P value*
R (min)	6.943±0.019	7.315±0.014	<0.001	7.262±0.012	6.996±0.021	<0.001
K (min)	1.927±0.009	2.402±0.007	<0.001	2.242±0.005	2.087±0.01	<0.001
α-angle (°)	62.739±0.092	57.367±0.066	<0.001	59.14±0.055	60.967±0.099	<0.001
MA (min)	63.612±0.079	60.392±0.057	<0.001	61.434±0.047	62.570±0.085	<0.001

*, analysis of variance was used for comparisons between the 2 samples. R, ranges of reaction time; K, coagulation time; α-angle, coagulation angle; MA, maximum thrombus consistency.

Table 6 Recommended reference ranges of thromboelastography for healthy adults in Beijing based on the study cohort

Variables	Young and middle-aged group		Elderly group	
	Men (n=9,962)	Women (n=3,939)	Men (n=2,427)	Women (n=1,380)
R (min)	5.2–10.2	5.0–9.5	4.8–9.9	4.9–9.4
K (min)	1.5–3.8	1.2–3.1	1.2–3.9	1.2–2.9
α-angle (°)	43.8–67.6	50.7–71.4	44.0–71.0	52.4–73
MA (min)	50.0–69.2	51.5–72.1	49.8–71.3	52.9–73.5

R, ranges of reaction time; K, coagulation time; α-angle, coagulation angle; MA, maximum thrombus consistency.

MA, suggesting slightly enhanced platelet function. These results differ from those of Ji *et al.* in their cohort of 137 volunteers (8). It is likely that these differences were mainly due to differences in sample size.

The findings of our study indicated that the elderly participants tended to be hypercoagulable and had relatively stronger activities in coagulation factors, fibrinogen, and platelet compared with those of the young and middle-aged participants, regardless of sex. Epidemiological studies have shown that elderly patients have a higher risk of cardiovascular disease (13,19). Taking venous thromboembolism as an example, its incidence is second only to myocardial infarction. The incidence rate of the general population is 1–5% per year and is highly correlated with age (9,20). The risk of venous thromboembolism in the elderly can be caused by multiple factors, such as surgical fixation, severe medical diseases, malignant diseases, and heart failure. However, after excluding the cumulative risk factors that can affect the incidence rate of venous thrombosis in the elderly, the risk of venous thrombosis was still positively correlated with age, suggesting that old age could be an independent factor in the pathogenesis of venous thromboembolism. It was reported that the levels of coagulation factors VIII, IX, and XI (FVII, FIX and FXI) increase significantly with age, which is related to the risk of venous thrombosis (21-24). Similarly, it was also reported that the TEG results of elderly patients tended to be hypercoagulable (25-28), which is consistent with our results. This is likely caused by physiological aging, the increase of related coagulation factors, and impaired fibrinolysis (29).

The findings of our study indicated that, compared with men of the same age group, women tended to have hypercoagulable TEG results, with higher levels of coagulation factors, fibrinogen, and platelet activities, regardless of age. Our results are consistent with previously published results (6,7,26,27,30). One possible reason for this is that estrogen increases thrombin production, which has been confirmed in studies of the therapeutic effect of exogenous estrogen (31-33). In their study, Wang *et al.* found that the level of coagulation factors in elderly women was relatively higher than that in elderly men (21). However, these findings contradicted clinical epidemiological data, which consistently show that women who were not on hormone replacement therapy have a lower risk of thrombosis and cardiovascular disease than men (34). In particular, premenopausal women generally have a lower risk of cardiovascular disease than men (34). Therefore, further research is necessary to evaluate the basic principles behind this contradiction.

One of the limitations of the present study was that the drug use of the study participants was unknown. The use of oral contraceptives or hormone replacement therapy is associated with increased thrombus intensity and venous thromboembolism risk (26), and the use of anticoagulants or antiplatelet drugs will affect TEG results (1). Another limitation was the low number of participants in the elderly group. Further research with a large elderly cohort is warranted.

In conclusion, our study found that the coagulation factor and fibrinogen function of TEG tend to be hypocoagulable in Beijing population, compared with the reference standards provided by previous reagent manufacturers. We proposed the reference range of TEG in Beijing area: R: 5.1–10 min, K: 1.3–3.8 min, α-angle: 44.9–70.2°, and MA: 50.4–71 min, the sample size was large and in line with the normal distribution, suggesting that it should be used as a reference standard in Beijing. On this basis, we established the reference range of different genders for young and middle-aged people and elderly people for reference, so as to apply TEG detection more accurately in clinical practice.

Acknowledgments

Funding: This work was supported by the Guokang Technology Project Foundation (grant No. Y2022003).

Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1731/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1731/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1731/coif). CW reports grant from the Guokang Technology Project Foundation (No. Y2022003). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of Electric Power Teaching Hospital (No. 2022-KY-03-01). Individual consent from participants for this retrospective analysis was waived.

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(English Language Editor: R. Scott)

Cite this article as: Wei C, Zhao JY, Wang SY, Sun HN, Guan NZ. Establishment of normal reference range for thromboelastography based on 17,708 cases in Beijing, China. Ann Transl Med 2022;10(10):550. doi: 10.21037/atm-22-1731