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Relation of thromboelastography parameters to conventional coagulation tests used to evaluate the hypercoagulable state of aged fracture patients

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Abstract

Fractures are common among aged people, and rapid assessment of the coagulation status is important. The thromboelastography (TEG) test can give a series of coagulation parameters and has been widely used in clinics. In this research, we looked at fracture patients over 60 and compared their TEG results with those of healthy controls. Since there is a paucity of studies comparing TEG assessments with conventional coagulation tests, we aim to clarify the relationship between TEG values and the values given by conventional coagulation tests.

Forty fracture patients (27 femur and 13 humerus) over 60 years old were included in the study. The change in their coagulation status was evaluated by TEG before surgery within 4 hours after the fracture. Changes in TEG parameters were analyzed compared with controls. Conventional coagulation test results for the patients, including activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen, and platelets, were also acquired, and correlation analysis was done with TEG parameters, measuring similar aspects of the coagulation cascade. In addition, the sensitivity and specificity of TEG parameters for detecting raised fibrinogen levels were also analyzed.

The K (time to 20 mm clot amplitude) and R (reaction time) values of aged fracture patients were lower than controls. The values for angle, maximal amplitude (MA), and coagulation index (CI) were raised compared with controls, indicating a hypercoagulable state. Correlation analysis showed that there were significant positive correlations between fibrinogen and MA/angle, between platelets and MA, and between APTT and R as well. There was significant negative correlation between fibrinogen and K. In addition, K values have better sensitivity and specificity for detecting elevated fibrinogen concentration than angle and MA values.

Aged fracture patients tend to be in a hypercoagulable state, and this could be effectively reflected by a TEG test. There were correlations between TEG parameters and corresponding conventional tests. K values can better predict elevated fibrinogen levels in aged fracture patients.

Abbreviations: APTT = activated partial thromboplastin time, AUC = area under curve, CI = coagulation index, INR = international normalized ratio, MA = maximal amplitude, PLT = platelets, ROC = receiver operating characteristics, TEG = thromboelastography, TPI = thrombodynamic potential index.

Keywords: fibrinogen, fracture, hypercoagulation, thromboelastography

1. Introduction

Rapid assessments of hemostatic function are essential in the management of bleeding due to trauma, major surgery, or hereditary hemorrhagic diseases.[1–3] As a global hemostatic test, thromboelastography (TEG) can give immediate results reflecting platelet function, thrombin generation, fibrinogen levels, and fibrinolysis and with bedside availability.[4,5] Thus, TEG has been successfully used for coagulation assessment in trauma and perioperative care and for bleeding assessment in hemophilic patients.[1–3]

A series of values can be derived from a TEG tracing.[6–8] Compared with the routine coagulation tests including activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen, and platelets, some of the TEG values describe similar aspects of the coagulation process. For example, R values can be compared with INR and APTT, since the endpoint of these tests is the detection of coagulation; and K, angle, and maximal amplitude (MA) values can be compared with platelet counts and fibrinogen concentration, since all these tests are involved in the initiation of coagulation and are associated with the final clot strength.[1–5] Since the measuring methods are extremely different, then the question is raised as to what extent the TEG parameters can reflect the changes of corresponding conventional tests.

Fractures are common among aged people and have a high mortality rate within 1 year after the fracture.[9,10] Evaluation of patients' coagulation function is important since the fractures may alter many of the patients' coagulation ability.[11] Enhanced clot formation on a TEG test may be associated with a

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hypercoagulable status.[12,13] Indeed, R time, K time, MA, and angle were found to have been changed in surgical patients as compared to in healthy controls.[12–14]

In this research, we aimed to analyze the TEG parameters of aged fracture patients and clarify their change of coagulation status before surgery. Since there are a paucity of studies comparing TEG assessments with conventional coagulation tests, we did a correlation analysis of the TEG parameters with INR, APTT, fibrinogen, and platelet values in order to clarify the relationship of TEG tests with conventional coagulation tests.

2. Materials and method

2.1. Patients

Forty fracture patients (27 femur and 13 humerus) over 60 years old were admitted to the hospital from September 2013 to February 2015. TEG tests were administered within 4 hours after the fracture and before surgery to check whether their coagulation status was suitable for surgery. Their medical records were collected with approval from the institutional ethical review board of Peking University People's Hospital. Forty healthy adults with matching ages were enrolled in the control group, all of whom had previously had physical examinations and selected TEG as a test for coagulation function, and their records were collected. All selected individuals had given informed consent and were without complications and chronic diseases and without medication intakes; and patients who were diagnosed with thromboembolic events afterwards were excluded in our research.

2.2. Blood sampling and TEG assay procedure

Venous blood was collected in the Vacutainer tubes (Becton Dickinson) containing 1/10 volume of 0.129 M sodium citrate. APTT, INR, and fibrinogen levels were measured by ACL TOP700 (Instrumentation Laboratory) with plasma from citrated blood. Platelet count was measured by Sysmex XE-2100 (TOA Medical Electronics, Kobe, Japan) with blood collected in Vacutainer K3-EDTA tubes (Becton Dickinson).

TEG test was performed within 2 hours after specimen collection and 1 mL of citrated blood was added to 1 vial of kaolin. After mixing gently by inversion, 340 μL of this solution was added to the standard specimen cup along with 20 μL calcium chloride (0.2 M). TEG was initiated using a Thromboelastograph Hemostasis analyzer (Haemoscope, Skokie, IL). Quality-control checks were performed according to the manufacturer's instruction.[15] We recorded TEG parameters including R, K, angle, MA, etc. R is the distance from the start of the tracing to the point where the lines have diverged 1 mm, which evaluates the intrinsic pathway.[15,16] K is the distance between the end of R and the point at which the distance between the 2 branches reaches 20 mm. The K is a measurement of the rapidity of clot development, the combined R and K values reflect the coagulation time from its beginning to predetermined clot strength.[17] MA is the maximal distance between the 2 diverging branches, reflecting final clot strength.[6] The angle (α) is measured between the midline and the tangent to the curve drawn from the 1 mm wide point. This angle is an indication of the rate of clot formation.[6] These 4 values can then be entered into a formula to derive the coagulation index (CI). $CI = 0.1227(R) + 0.0092(K) + 0.1655(MA) - 0.0241(\alpha) - 5.0220$.[18,19] Normal CI in humans is −3.0 to 3.0. Values above 3.0 are considered hypercoagulable, while values below −3.0 is hypocoagulable.[19] A typical hypercoagulable TEG tracing shows decreased R and K, and increased MA and angle.[19]

2.3. Statistics

GraphPad Prime 5.5 was used for the calculation of all tests. Mann–Whitney *U* test was performed to compare each parameter between the 2 groups. Pearson correlation coefficient (*r*) was estimated for the conventional coagulation tests and TEG parameters that followed a normal distribution. For correlations with INR which follows a discrete distribution, Spearman correlation test was used. *P* values for the respective correlation coefficients were calculated using F-tests. In order to exemplify the correlations, we then calculated the diagnostic sensitivities and specificities of TEG parameters for detecting elevated fibrinogen level (>400 mg/dL). Receiver operating characteristics (ROC) curves of MA, K, and angle were also analyzed and area under curve (AUC) was used to compare the ROC curves. *P* values less than 0.05 are regarded as significant.

3. Results

3.1. TEG values were altered among aged fracture patients

We did TEG tests with citrated blood from 40 aged fracture patients and a control group. Four major TEG parameters including R, K, angle, and MA were measured. In addition, other TEG indexes including clot firmness (G, shear elastic modulus strength), elasticity constant (E), and thrombodynamic potential index (TPI, defined as MA • 100 [100–MA]/2 • K) were also measured.[18,19] All the results are listed in Table 1. We found that values of TEG parameters were altered in aged fracture patients. The K value (1.285 ± 0.584 minutes) and R value (5.065 ± 1.131 minutes) were lower in old fracture patients than in the control (K, 1.628 ± 0.367 minutes; R, 6.498 ± 1.230 minutes), and angle (70.58° ± 7.40°), G (10918 ± 3329 d/sec), E (218.4 ± 66.6 d/sec), TPI (100.40 ± 47.80/sec), MA (67.13 ± 7.41 mm), and CI (1.998 ± 2.032) values were raised compared with in the control (angle, 65.75° ± 4.52°; G, 8221 ± 1368 d/sec; E, 164.4 ± 27.7 d/sec; TPI, 53.37 ± 17.25/sec; MA, 61.76 ± 4.12 mm; CI, −0.095 ± 1.360). All these changes of parameters represent a hypercoagulation status for aged fracture patients.

Table 1

Comparison of thromboelastography parameters between the fracture group and the control group.

Characters	Unit	Reference interval	Control (n = 40)	Fracture (n = 40)	*P*
Male/female	N/A	N/A	13/27	15/25	0.8149
Age	year	N/A	78.3 ± 7.3	80.2 ± 6.1	0.2129
R	minute	5–10	6.498 ± 1.230	5.065 ± 1.131	<0.001
K	minute	1–3	1.628 ± 0.367	1.285 ± 0.584	<0.001
MA	mm	50–70	61.76 ± 4.12	67.13 ± 7.41	<0.001
Angle	°	53–72	65.75 ± 4.52	70.58 ± 7.40	<0.001
CI	N/A	−3–3	−0.095 ± 1.360	1.998 ± 2.032	<0.001
G	d/sec	4500–11,000	8221 ± 1368	10918 ± 3329	<0.001
E	d/sec	92–218	164.4 ± 27.7	218.4 ± 66.6	<0.001
TPI	/sec	5–90	53.37 ± 17.25	100.40 ± 47.80	<0.001

Data are presented as mean ± SD, and Mann–Whitney *U* test was performed to compare each parameter between the 2 groups. CI = coagulation index, MA = maximal amplitude, N/A = not available, SD = standard deviation, TPI = thrombodynamic potential index.

3.2. Thromboelastography of aged fracture patients reflects a hypercoagulable status

We observed the TEG tests of the aged fracture group and the control group, and found that the graphs showed significant differences. Representative TEG tests of fracture patients and health controls are shown in Fig. 1A. We found that the increased MA makes the TEG graphs of aged fracture patients broader than normal graphs. The decreased R and K values shortened the initial part of the TEG test. The differences of 4 major TEG parameters between the 2 groups, including R, K, angle, and MA, are shown in Fig. 1B. These changes mean that the aged fracture patients are under a hypercoagulation status.[19] Therefore, we

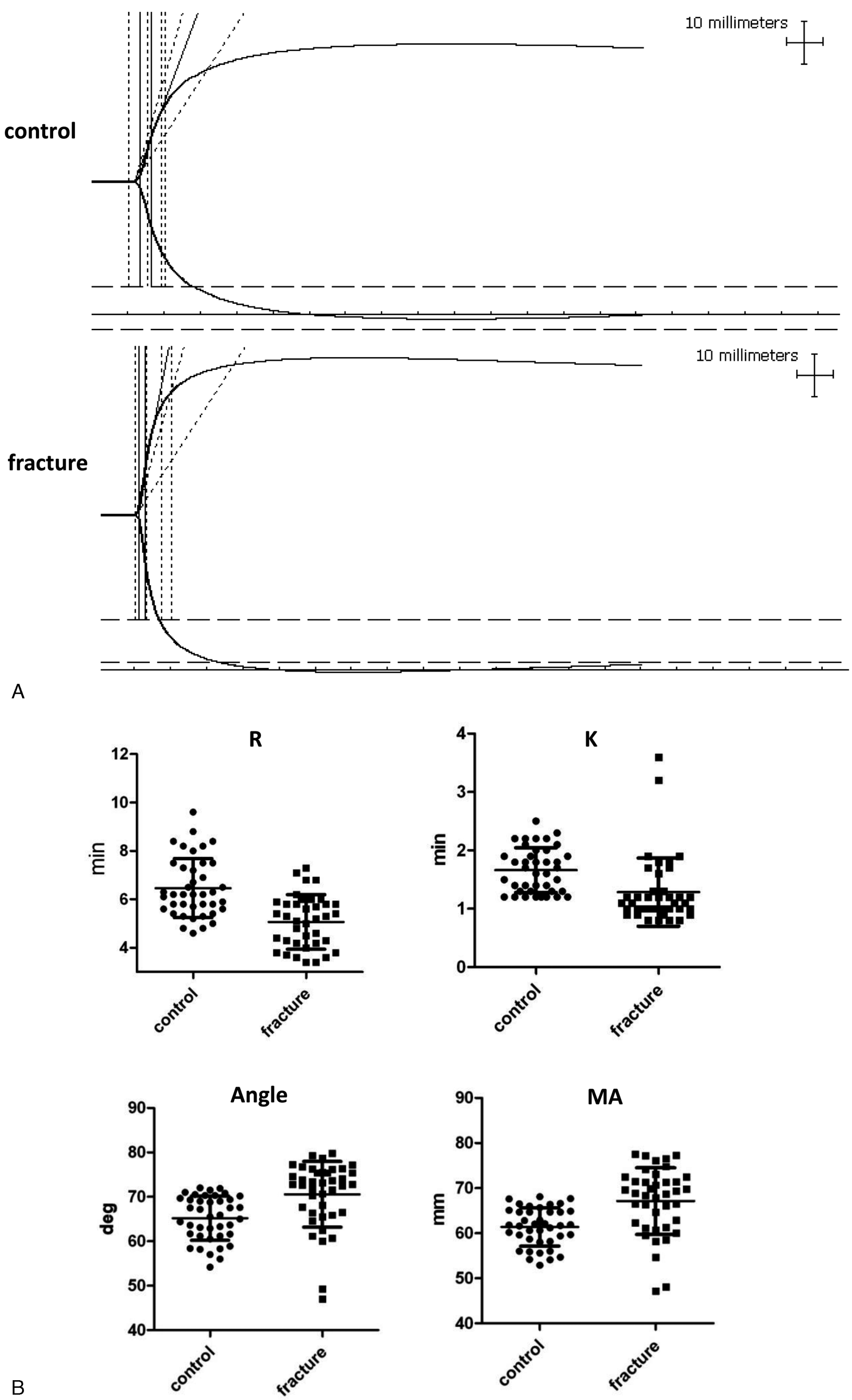

Figure 1. Comparison of thromboelastography of fracture patients and healthy control. (A) Represented thromboelastography of fracture patients and the controls. (B) Comparison of four major TEG parameters of the 2 groups. Data are present as mean ± SD. SD = standard deviation, TEG = thromboelastography.

can conclude from the TEG intuitively that aged fracture patients are undergoing a hypercoagulation status after the fracture and before surgery.

3.3. Correlation analysis of the TEG parameters with conventional coagulation tests

Although TEG tests are becoming more widely used, conventional coagulation assays, including fibrinogen, INR as well as APTT, remain common in clinics. However, there was a lack of studies comparing TEG assays with conventional coagulation tests. So, we did a correlation analysis to find the relationship between TEG tests and conventional tests in aged fracture patients. The statistics for conventional tests of the 2 groups are listed in Table 2. We found that levels of fibrinogen were higher in the fracture group, which is in accordance with our previous research. For other tests the differences were not so obvious.[20]

Correlation analysis of the fracture group was carried out for values that were regarded to be measuring similar aspects to those of the coagulation cascade. R was compared with INR and APTT, since the endpoint of these tests is the detection of coagulation. Platelet count and fibrinogen concentration were compared with K, angle, and MA, since these tests are involved in the initiation of coagulation and are associated with the final clot strength.[1–5]

The correlation results are shown in Fig. 2. Correlation analysis shows that there are significant positive correlations between fibrinogen and MA ($r=0.3910$, $P=0.0126$) or angle ($r=0.4246$, $P=0.0063$), between platelets and MA ($r=0.4078$, $P=0.0090$), and between APTT and R ($r=0.3327$, $P=0.0360$) as well. There is significant negative correlation between fibrinogen and K ($r=0.5602$, $P=0.0002$). We did correlation analysis between INR and R, between platelets and angle, and between platelets and K, the P values are 0.44, 0.30, and 0.74 meaning these correlations are not significant.

3.4. K value has better sensitivity and specificity for detecting elevated fibrinogen concentration

In order to accentuate the correlations, we analyzed the sensitivity and specificity of the TEG parameters for detecting the change of levels of conventional tests. For fibrinogen, concentrations over 400 mg/dL are regarded as elevated levels according to the reference range of Chinese people. For platelets and APTT, since most of the values are within normal ranges, we are not able to analyze the sensitivity and specificity of TEG parameters to detect the abnormality.

The sensitivity to detect fibrinogen above 400 mg/dL was 0.4167 with MA, 0.6667 with angle, and 0.5 with K. The specificity to detect fibrinogen above 400 mg/dL was 0.6429 with MA, 0.4643 with angle, and 0.8929 with K, as listed in Table 3.

Table 2

Conventional coagulation parameter analysis of 2 groups.

Characters	Unit	Reference interval	Control (n=40)	Fracture (n=40)	P
APTT	second	25.4–38.4	32.05±3.19	31.22±3.36	0.17
INR	–	1–3	1.037±0.083	1.063±0.067	0.08
FIB	mg/dL	200–400	298.3±73.0	352.9±90.6	0.0045
PLT	$\times 10^9$/L	125–350	189.5±52.6	212.1±62.9	0.10

Data are presented as mean±SD, P values were measured by performing Mann–Whitney U test between the 2 groups. APTT=activated partial thromboplastin time, FIB=fibrinogen, INR=international normalized ratio, PLT=platelets.

ROC curves for the performance of MA, angle, and K in detecting elevated levels of fibrinogen (greater than 400 mg/dL) are shown in Fig. 3, and the AUC and 95% confidence interval are listed as well. Accordingly, we found that K values were with the largest AUC value at 0.70. Although this is not quite high, it could still prove that K values have better sensitivity and specificity than MA and angle values for detecting elevated fibrinogen concentration. From these results, we conclude that some of the TEG parameters are capable of reflecting the levels of relevant conventional tests that measure similar aspects of the coagulation process, including fibrinogen, APTT, and platelets to a certain degree.

4. Discussion

In this study, we demonstrated that for aged fracture patients, TEG tests can reflect coagulation status dynamically with a series of related values. According to the TEG results, we further demonstrated that aged fracture patients tend to be in hypercoagulation status before surgery, with decreased R and K and increased MA and angle. We also compared TEG assays with conventional coagulation tests and found there were significant positive correlations between fibrinogen and MA/angle, between platelets and MA, and between APTT and R. There was significant negative correlation between fibrinogen and K. By analyzing ROC curves, we found that K values are better for detecting elevated fibrinogen concentration than angle and MA values in aged fracture patients.

Early detection of coagulation abnormality after injury is a valuable prognostic factor for blood transfusions and death.[12,13] Fibrin clots formed at the site of injury are necessary for limiting hemorrhaging and for subsequent survival.[1] The hypercoagulable state has been reported in the early stages of trauma.[21,22] This was mainly thought to result from tissue injury and related inflammation, which has been attributed to elevated thrombin generation unregulated by tissue factor.[23,24] Here, we paid attention to fractures, a common injury for aged patients, and the coagulation status was measured by TEG within 4 hours of the fracture. After the fracture occurs, there is an acute phase reaction with an increase in platelet activity and fibrinogen levels, and in our opinion this acute phase reaction produces hypercoagulative TEG patterns.[25,26]

TEG could provide a good assessment of the hypercoagulation status of aged fracture patients in the surgery department. TEG accurately records the kinetic process of clot formation during blood coagulation. And it is useful in several aspects of managing abnormalities in aged fracture patients, which are unique advantages of the TEG test.[4,5] The routine coagulation tests, including fibrinogen, prothrombin time, and APTT, are still widely used in hospitals, though they do not give information about the overall strength of the clot or the rate of the turnover of the clot formed. So, are TEG tests capable of completely reflecting the situations represented in conventional coagulation tests? Ågren et al[18] have researched patients before and after different kinds of surgery and inquired into the correlation between TEG and conventional tests, and they concluded that the agreement between them was poor for these patients. From our results, we can see that in aged fracture patients before surgery and within 4 hours of the fracture, the TEG parameters to some extent are in correlation with specific conventional coagulation tests, for example, K and fibrinogen, R and APTT, etc. But the correlation is not strong. Considering that the principles of the tests are completely different, these results are not beyond our expectation.

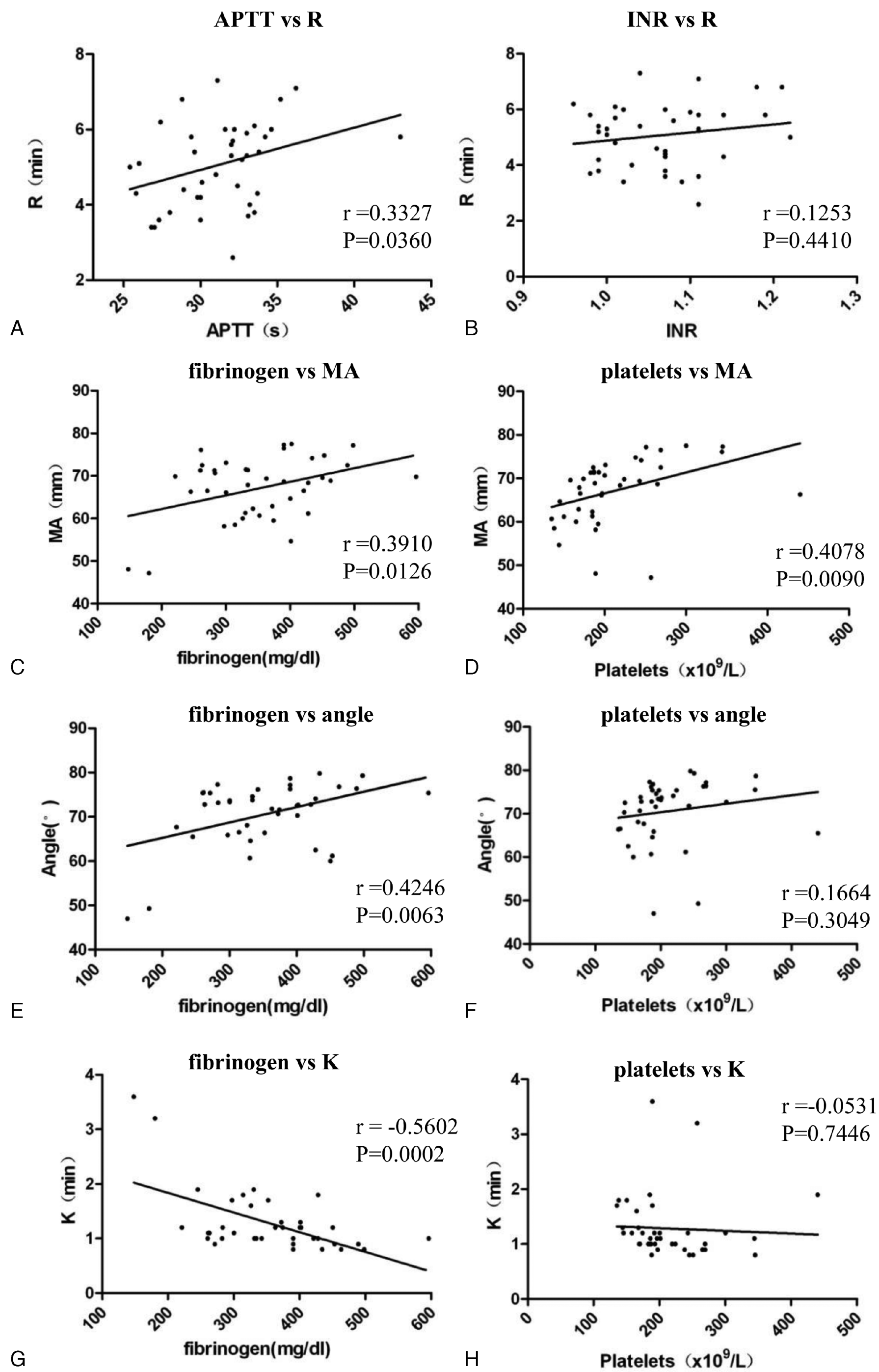

Figure 2. Correlation analysis between TEG parameters and conventional coagulation tests of aged fracture patients. (A) APTT and INR versus TEG R value. Data are present as plots with linear fit, Pearson test *r* and *P* values are listed. (B) INR versus TEG R value. Spearman test *r* and *P* values are listed. (C, D, G) Fibrinogen concentration versus TEG MA (C), angle (E), and K (G) values. Scatter plots with linear fit are shown and Pearson *r* and *P* values are listed. (D, F, H) Platelet count versus TEG MA (D), angle (F), and K (H) values. Data are present as Scatter plots with linear fit, Pearson test *r* and *P* values are listed. *P* values less than 0.05 are regarded as significant. APTT = activated partial thromboplastin time, INR = international normalized ratio, MA = maximal amplitude, TEG = thromboelastography.

Table 3

Sensitivity and specificity analysis of TEG parameters for detecting fibrinogen levels over 400 mg/dL.

TEG parameters	Standard	Sensitivity	95%CI	Specificity	95%CI
MA	>70 mm	0.4167	0.1517–0.7233	0.6429	0.4406–0.8136
Angle	>72°	0.6667	0.3489–0.9008	0.4643	0.2751–0.6613
K	<1 minute	0.5	0.2109–0.7891	0.8929	0.7177–0.9773

CI = confidence interval, MA = maximal amplitude, TEG = thromboelastography.

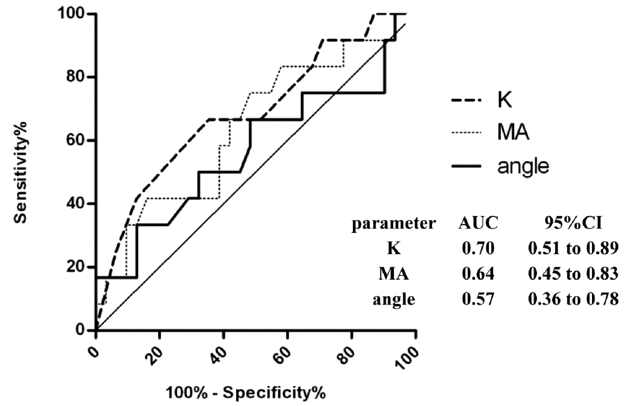

Figure 3. ROC curve of TEG parameters for detecting raised concentration of fibrinogen. ROC curves detecting elevated level of fibrinogen (>400 mg/dL) by K, MA, and angle (α) values are present. The AUC and 95%CI are listed. AUC = area under curve, CI = confidence interval, MA = maximal amplitude, ROC = receiver operating characteristics, TEG = thromboelastography.

One limitation of present research is that the research is based on a small group of patients. There are limited numbers of aged fracture patients admitted to the hospital. But according to the results, the differences are quite significant between the 2 groups. Further multicentered research should be done to better support our conclusions. In the end, our results give a good reference for physicians to evaluate the results of TEG tests and conventional coagulation tests, which will be beneficial to fracture patients.

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