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Characterization of thromboelastography of patients with different pathological types of nephrotic syndrome

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Abstract

To investigate the changes in blood coagulability as measured by thromboelastography (TEG) in patients with nephrotic syndrome of different etiologies as well as in patients with venous thromboembolic events (VTE).

From January 2013 to October 2017, patients who were diagnosed as idiopathic membranous nephropathy (IMN), minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) were enrolled into this retrospective study in which their clinical characteristics, including TEG variables, were investigated. According to the presence or absence of VTE, the patients with IMN were divided into 2 groups of VTE and non-VTE. The risk factors of VTE were analyzed with logistic regression.

Significant differences in TEG parameters were found among the 3 groups of patients with R and K values lower, while the α-angle, maximum amplitude (MA) and confidence interval (CI) values higher, in the IMN group than those in the MCD and FSGS groups ($P < .01$). Multiple linear regression analysis indicated that the histologic subtype was an independent relevant factor of K time, angle, MA, and CI values. Multivariate logistic regression analysis revealed that serum albumin and CI value were independent risk factors of VTE ($P < .05$).

The results showed that IMN patients may have higher whole blood coagulability than MCD and FSGS patients. The hypercoagulability in IMN patients may be attributed to platelet hyperactivity and the accelerated fibrin-platelet interaction. Hypoproteinemia and increased CI value were independent risk factors of VTE in IMN.

Abbreviations: NS = nephrotic syndrome, TEG = thromboelastography, VTEs = venous thromboembolic events.

Keywords: idiopathic membranous nephropathy, nephrotic syndrome, pathological type, TEG, venous thromboembolism

1. Introduction

Nephrotic syndrome (NS) is 1 condition typically associated with hypercoagulability. Hypercoagulability has been implicated in venous thromboembolic events (VTEs) which are associated with

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increased morbidity and mortality in NS.[1] The reported incidence of VTE in NS varies from 2% to 42% depending in different case series or pathological types of NS, among which idiopathic membranous nephropathy (IMN) has the highest incidence rate.[2] Kerlin and colleagues found that the VTE incidence in IMN may be as high as 37% while the cumulative incidence was only about 21% in other common pathological types of NS, including minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) based on different case series.[2]

Studies have shown that urinary loss of anticoagulants (eg, antithrombin III, protein C and protein S), increased synthesis of procoagulant factors (eg, factors V, VIII) and fibrinogen in response to hypoalbuminemia, and platelet hyperreactivity all contribute to the hypercoagulability in NS patients.[3] At present, the reasons for differential coagulabilities among the different pathological types of NS are still not fully understood. In constrast with the conventional coagulation assessment that examines only certain aspects or parameters of hemocoagulation process, thromboelastography (TEG) monitors the global process of coagulation and thus reflects the dynamic nature of coagulation. TEG is especially useful in assessing hypo or hypercoagulable state under complex and multifactorial conditions.[4] Previous studies have well demonstrated the usefulness of TEG in assessing hypercoagulability in the patients of pregnancy, postoperation, and certain types of NS, although the sizes of the studies were small.[5–8]

Since the incidence of VTE differs among patients with various NS histopathologies and thrombosis confers a high risk of morbidity and mortality, it is important to assess the coagulation of the NS patients of different pathological types, including those with VTE, by using TEG. Such that we may reveal the difference in hypercoagulable state among NS patients of different types and

identify the risk factors of hypercoagulability and VTE. Such studies may also be able to determine whether it is feasible to use TEG to predict occurrence of VTE in patients, possibly helping clinicians in treating the patients.

2. Materials and methods

2.1. Patients

This study retrospectively involved in patients with NS who had undergone renal biopsy with the diagnosis of IMN, MCD and FSGS at our hospital and had taken TEG examination from January 2013 to October 2017.LOA2 The inclusion criteria:

(1) The histologic and immunopathologic changes were consistent with idiopathic glomerulonephritis (IMN, MCD and FSGS), and no secondary causes, such as systemic lupus erythematosus, hepatitis B and tumor, were found;
(2) proteinuria was greater than 3.5 g/24 hOUR, and serum albumin level less than 30 g/L.

The exclusion criteria:

(1) Age≦18 years old;
(2) Use of oral contraceptives or anticoagulants within 48 hours and antiplatelet drugs within 1 week prior to blood and urinary samples collections for laboratory tests;
(3) a history of VTE, exposure to classic risk factors for VTE (such as acute infection), presence of major surgery, prolonged (6 weeks) immobilization and pregnancy (<3 months);
(4) treatment with plasma or albumin infusion, plasma exchange, or hemodialysis.

A total of 452 IMN patients, 106 MCD patients and 155 FSGS patients met the the diagnostic criteria for NS and received TEG examination. According to the exclusion criteria, in total, 190 NS patients with IMN, 41 NS patients with MCD and 52 NS patients with FSGS were included, while 81 patients with IMN who had urinary protein≤1 g/24 hour when TEG was detected before renal biopsy as controls. The IMN patients were stratified into 2 groups, VTE group and non-VTE group according to the presence or absence of VTE. There were 16 IMN patients with VTE and 174 IMN patients without VTE.LOA1 A description of the study flow is depicted in Fig. 1. This study was approved by the institutional review board of Jinling Hospital of Nanjing University, and all renal-biopsy-patients had signed the informed consent of Renal Clinical Database Establishment when hospitalized, allowing their data for clinical research.

2.2. Clinical parameters

The medical records of following parameters were collected for the study: age, gender, serum creatinine, albumin, cholesterol, triglycerides, platelet count (PLT), hemoglobin, and 24 hour urine protein. In addition, the results of coagulation tests, including prothrombin time, activated partial thromboplastin time, serum antithrombin III level, and fibrinogen, were also collected. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.[9]

2.3. TEG parameters

The haemostatic process was recorded and analyzed with a TEG 5000 thromboelastograph analyzer. For TEG analysis, the whole blood was collected to a vacutainer containing 3.2% sodium citrate, and then 1 ml of the citrated whole blood was added to a tube
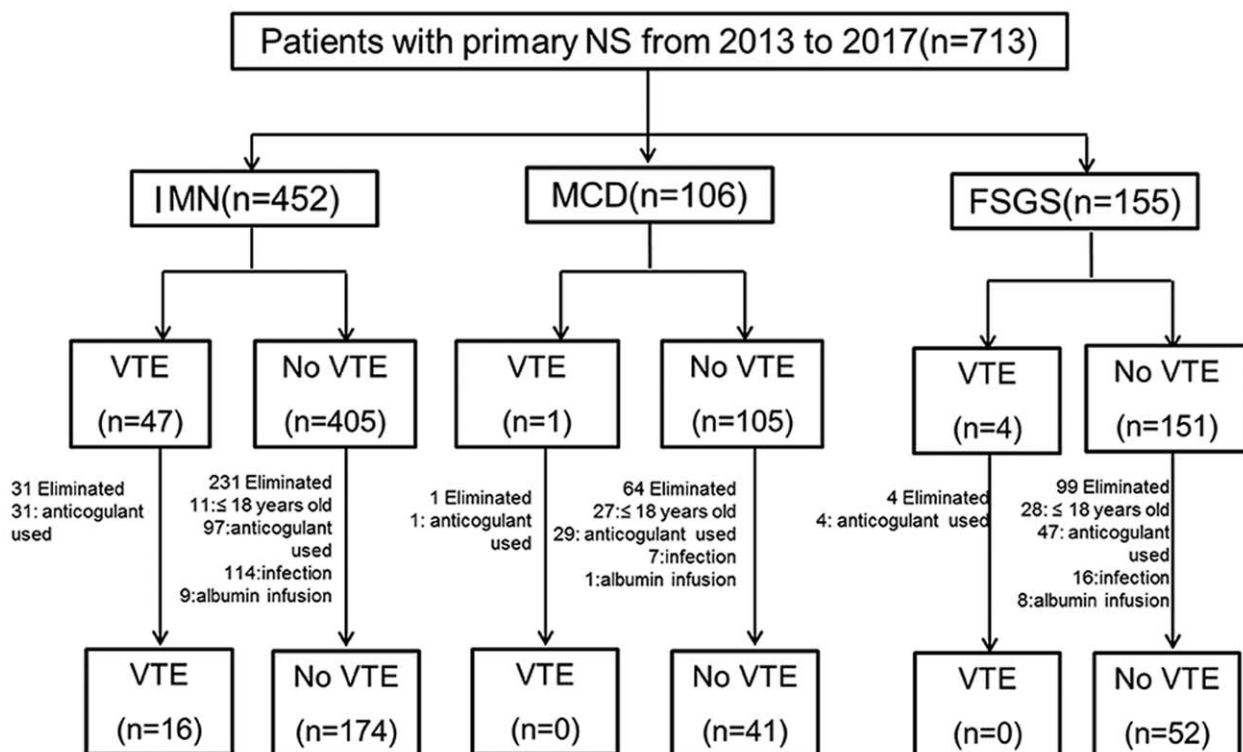
Figure 1. The flow chart of this study. FSGS = focal segmental glomerulosclerosis; IMN = idiopathic membranous nephropathy; MCD = minimal change disease; VTE = venous thromboembolic events.

containing 1% kaolin. An aliquot of 340 μL sample was transferred to a TEG cup to which 20 μL calcium chloride (0.2 mol/L) was preloaded for recalcification, and then the clotting test was started.

The following thromboelastographic variables were recorded:

(1) Reaction time (R), the time from the start of the test to initial fibrin formation (a TEG amplitude of 2 mm), which represents the rate of initial fibrin formation, related to the function of coagulation factors with the normal range of 5 to 10 minutes;
(2) Kinetics-time (K), the period from the R time to the time when the amplitude of curves reaches 20 mm, which measures the velocity of of clot formation and reflects the interaction of platelets and fibrinogent (normal range, 1–3 minutes);
(3) Alpha-angle(α-angle), the angle between the tangent line (drawn from the point to the curve) and the horizontal baseline, which is influenced by the factors the same as K time and represents the kinetics of fibrin buildup and cross-linking (normal range, 53–72°);
(4) Maximum amplitude (MA), the greatest amplitude of the TEG tracing and indicative of the ultimate strength of the fibrin clot which is mainly reflects platelet function and is influenced by the quantity and quality of platelets (normal range, 50–70 mm);
(5) Coagulation index (CI), which is derived from the above 4 values and represents the overall coagulation profile (normal range, -3-+3).

2.4. Diagnosis of thromboembolic events and hypercoagulable state

We only considered the objectively verified thromboembolic events, including pulmonary embolism (PE), deep vein thrombosis (DVT) and renal vein thrombosis (RVT). PE was confirmed by computed tomography pulmonary angiography, DVT by compression ultrasound or venography, RVT by computed tomography venography or doppler ultrasound. A hypercoagulable state was defined as an abnormality of 2 or more of the TEG values (shortened R time, shortened K time, increased α-angle, and increased MA).[10–12]

2.5. Statistical analysis

Data analysis was performed using the software SPSS version 22.0 (SPSS Inc. Chicago, IL). Continuous data was expressed as the mean ± standard deviation or medians (ranges), while categorical data was expressed as the frequency or percentage. For continuous data, differences were assessed by Student t test, ANOVA, Mann-Whitney U test and Kruskal-Wallis test depending on the normality of the data and levels of the outcome variable. Categorical data was compared using the χ^2 test. Pearson and Spearman correlation coefficient were used to assess the relationship between TEG parameters and other clinical variables. Multivariate linear regression and logistic regression analysis were performed to assess whether pathological type predicts hypercoagulability as the dependent variable. Univariate and multivariate logistic regression analysis were used to assess risk factors associated with VTE in patients with MN. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of a certain index for VTE. A 2-tailed value of $P < .05$ was regarded as statistically significant.

3. Results

3.1. The baseline characteristics

A total of 283 patients were enrolled in this study, including 190 diagnosed with IMN, 41 diagnosed with MCD, and 52 diagnosed with FSGS. Baseline characteristics were described in Table 1. The median age was 43 years old (30–56 years).

Table 1

Comparison of baseline characteristics among groups.

	All (n=283)	Controls (n=81)	IMN (n=190)	MCD (n=41)	FSGS (n=52)	P**
Age, yr	43.8±15.5	47.4±14.6	47.3±14.2[b,c]	30.9±11.9[a]	35.4±15.7[a]	<.001
Gender (%male)	74.7%*	40.7%	68.4%	53.7%	71.2%	.13
Serum albumin (g/L)	25.3 (22.5,27.9)*	37.4 (32.2,41.4)	25.9 (23.8,28.1)[b,c]	22.60 (19.9,26.8)[a]	23.2 (20.8,25.7)[a]	<.001
eGFR[ml/(min 1.73m2)]	96 (76,111)*	106 (94,114)	97 (80,110)[b,c]	113 (94,123)[a,c]	68 (39,97)[a,b]	<.001
Serum cholesterol (mmol/L)	9.7 (7.8,11.8)*	6.0 (4.8,7.5)	9.1 (6.3,11.2)[b,c]	11.8 (10.0,13.8)[a]	11.8 (8.6,13.7)[a]	<.001
Serum triglycerides (mmol/L)	2.4 (1.8,3.4)*	1.5 (1.2,2.1)	2.4 (1.3,3.2)[c]	2.4 (2.0,3.6)	2.8 (2.2,4.0)[a]	.02
PLT (×10⁹/L)	257.3±86.5	253.3±53.7	257.7±85.5	258.7±87.8	254.1±92.5	.96
Hemoglobin (g/L)	137.6±21.4*	132.9±17.1	135.5±20.1[b]	147.3±18.9[a]	140.7±27.2	.002
Proteinuria (g/24h)	7.0 (5.1,10.0)*	0.7 (0.6,0.9)	6.9 (5.0,9.6)[c]	7.0 (4.9,10.9)	8.6 (5.7,13.1)[a]	.01
PT (s)	10.1±1.0	10.2±0.67	9.9±1.0[b,c]	10.5±0.8[a]	10.3±0.9[a]	<.001
APTT (s)	32.6±5.9	32.2±4.37	32.1±5.1[b]	35.5±6.2[a]	33.6±7.1	.001
fibrinogen (mg/dL)	476.1±107.7*	348.0±71.85	462.6±106.2[b,c]	527.7±79.1[a]	503.0±11.6[a]	<.001
TEG parameters						
R (min)	6.3±1.3	6.1±1.04	6.2±1.2[b,c]	6.8±1.5[a]	6.5±1.4[a]	.002
K (min)	1.2 (1.0,1.4)*	1.5 (1.2,1.9)	1.2 (1.0,1.)[b,c]	1.3 (1.1,1.5)[a]	1.3 (1.1,1.6)[a]	.001
α-angle (°)	72.4 (69.3,75.1)*	69.0 (64.1,72.1)	72.9 (69.9,75.7)[b,c]	69.9 (66.8,73.5)[a]	70.3 (68.0,73.5)[a]	<.001
MA (mm)	70.7±5.1*	65.1±6.0	71.1±5.1[c]	70.7±4.3[c]	68.4±6.3[a,b]	.002
CI	1.7±1.40*	0.8±1.41	1.9±1.3[b,c]	1.1±1.4[a]	1.2±1.5[a]	<.001

APTT = activated partial thromboplastin time, CI = confidence interval, FSGS = focal segmental glomerulosclerosis, IMN = idiopathic membranous nephropathy, K = kinetics time, MA = maximum amplitude, MCD = minimal change disease, MN = membranous nephropathy, PLT = platelet count, PT = prothrombin time, R = reaction time, TEG = thromboelastography.
* $P < .05$, All vs control group.
** Patients with MN vs MCD vs FSGS.
a $P < .05$, vs MN group.
b $P < .05$, vs MCD group.
c $P < .05$, vs FSGS group.

Among the patients, 245 were males and 118 were females. The median proteinuria was 7 g/24 hours (5.1–10.0 g/24 hours) and serum albumin 25.3 g/L (22.5–27.9 g/L). Several parameters differed significantly among subgroups, including older age and less severe proteinuria, hypoalbuminemia and hyperlipidemia in the IMN group. There was a higher number of platelet counts in patients with IMN, however, the difference did not reach a statistical significance.

3.2. Comparisons of TEG parameters among the NS patients of different pathological types

The TEG analysis indicated a hypercoagulable state in the IMN group compared to the MCD and FSGS groups ($P < .001$) (Table 1) as evidenced by shorter R-time ($P = .002$) and K-time ($P = .001$), wider α-angle ($P < .001$), and greater CI values ($P < .001$) in the IMN group vs MCD and FGSG groups. There was no other difference in the TEG values between MCD and FSGS groups except that FSGS group had a higher MA value compared with the MCD group ($P = .047$).

The results of multivariate analysis to identify disease-specific risks for hypercoagulability are shown in Table 2. The underlying pathological types were associated with hypercoagulability. The IMN patients had a higher risk of hypercoagulability (odds ratio [OR]:3.29, 95% confidence interval [CI]:1.57–6.92, $P < .01$) compared with FSGS patients (reference group). The risk of hypercoagulability in MCD patients was higher than that of FSGS, but the difference did not reach a statistical significance (OR:1.36, 95%CI: 0.54–3.48, $P = .52$).

Correlation and linear regression analysis were performed to evaluate the relationship between TEG parameters and relevant clinical variables using data from the 190 patients diagnosed with IMN. The results showed that serum albumin was inversely correlated with MA and CI values (r = −0.15, $P = .02$; r = −0.14, $P = .04$). Multivariate linear regression analysis with age, gender, serum albumin, PLT, Hb, fibrinogen, eGFR and histological diagnosis as independent variables, was also performed, and the results showed that IMN group had higher α-angle and CI values and a lower K time compared with the MCD group, and higher α-angle, MA and CI values and a lower K time compared with FSGS group (data not shown).LOA5

3.3. The incidence of VTE and characteristics of TEG parameters in patients with IMN

In the patients diagnosed with NS and underwent TEG test, VTE was found in 47 IMN patients (10.4%), 1 MCD patient (1.5%)

Table 2

Multivariable logistic regression analysis of risk of hypercoagulability in patients with IMN (abnormal TEG vs normal TEG).

	OR	95%CI	P
Age	1.02	1.00–1.04	.04
Female sex	2.81	1.66–4.77	<.001
PLT	1.00	1.00–1.01	<.001
Serum albumin	0.90	0.84–0.97	.01
Underlying disease			<.001
FSGS	1.00		
MCD	1.36	0.54–3.48	.52
IMN	3.29	1.57–6.92	<.001

CI = confidence interval, FSGS = focal segmental glomerulosclerosis; IMN = idiopathic membranous nephropathy; MCD = minimal change disease, OR = odd ratio, PLT = platelet count, TEG = thromboelastography.

Table 3

Comparison of clinical features between patients with VTE and without VTE in IMN.

	With VTE (n = 16)	Without VTE (n = 174)	P
Age, yr	52.4 ± 11.7	47.0 ± 14.2	.15
Gender (%male)	13 (81.3%)	116 (66.7%)	.23
Serum albumin (g/L)	23.2 (18.5,27.0)	26.0 (23.9,28.1)	.01
eGFR[ml/(min 1.73m2)]	85 ± 19	94 ± 26	.78
Serum cholesterol (mmol/L)	10.1 (6.6,11.8)	9.0 (7.6,10.7)	.74
Serum triglycerides (mmol/L)	2.4 (1.7,3.9)	2.4 (1.7,3.2)	.61
PLT (×10⁹/L)	256.3 ± 103.5	255.1 ± 84.1	.93
Hemoglobin (g/L)	130.2 ± 16.4	137.1 ± 20.1	.23
Proteinuria (g/24h)	8.5 (6.2,10.4)	6.4 (4.7,9.8)	.14
PT (s)	10.4 ± 2.0	9.9 ± 0.9	.40
APTT (s)	32.1 ± 4.3	32.3 ± 5.5	.90
fibrinogen (mg/dL)	481.7 ± 135.2	468.7 ± 105.8	.67
AT-III (%)	105.8 ± 25.7	108.5 ± 18.6	.64
R (min)	5.6 ± 1.2	6.2 ± 1.1	.04
K (min)	1.6 (0.8,1.3)	1.2 (1.0,1.5)	.02
α-angle (°)	74.8 (70.8,78.4)	72.6 (69.6,75.0)	.02
MA (mm)	73.8 ± 7.3	70.8 ± 4.7	.13
CI	2.9 ± 1.3	1.9 ± 1.3	<.001

APTT = activated partial thromboplastin time, CI = confidence interval, eGFR = estimated glomerular filtration rate, IMN = idiopathic membranous nephropathy, K = kinetics time, MA = maximum amplitude, PLT = platelet count, PT = prothrombin time, R = reaction time, VTE = venous thromboembolic event.

and 4 FSGS patients (2.6%). Renal vein thrombosis (RVT) was found in 36 IMN subgroup and none of those in MCD or FSGS subgroup. PE was found in 32 IMN patients, 1 MCD patient and 4 FSGS patients. Because 31 IMN patients use oral contraceptives and anticoagulants within 48 hours and antiplatelet drugs within 1 week prior to TEG analysis, they were excluded from the final study and only 16 IMN patients were enrolled. The median time from NS onset to VTE was 5.8 months (0.13–16 months). According to the presence or absence of VTE, the IMN patients were divided into 2 groups of VTE and non-VTE. As shown in Table 3, patients with VTE tended to be older and males had a higher chance to develop VTE, but both did not reach statistical significance. Hypoalbuminemia and proteinuria were more severe in patients with VTE than patients without VTE. The comparison of TEG parameters between the 2 groups showed that the patients in VTE subgroup had higher α-angle and CI values, lower R-time and K-time than the patients in non-VTE subgroup. No significant difference was found between the 2 groups in MA value.

3.4. The risk factors for VTE in IMN

Both the CI in TEG (OR:1.89; 95% CI: 1.25–2.88; $P < .01$) and serum albumin (OR: 0.81; 95% CI, 0.72–0.93; $P < .01$) were univariate predictors of VTE. The association between proteinuria and VTE did not achieve statistical significance ($P = .17$). In a multivariate analysis, both CI and serum albumin still independently predicted VTE.

ROC curve analysis showed that a threshold of 21 g/L (albumin) yielded a sensitivity of 43.75% and a specificity of 93.49%; while a threshold of 2.3 (CI) yielded a sensitivity of 68.75% and a specificity of 65.29%. The area under the ROC curve (AUC) value for combination of albumin and CI (mean AUC for albumin combined with CI: 0.734; 95% CI: 0.577–0.891) was greater than that of albumin (mean AUC for serum

albumin: 0.689; 95% CI: 0.689, 0.533–0.845) and CI (mean AUC for CI: 0.712; 95% CI: 0.588–0.835) alone, but both did not reach statistical significance.

4. Discussion

It is widely acknowledged that VTE, as a common complication of NS, is severe and consumes considerable amounts of health care resources.[1] Several factors may contribute to hypercoagulability and thus VTE in NS although they are not fully understood yet. These include decreased concentrations of anticoagulant factors, activation of procoagulant factors, abnormal fibrinolytic activity, and platelet hyperactivity. Besides, pathological type of NS has been thought to play a part in the VTE as suggested by a study in which IMN appeared to be at greatest risk for VTE compared with other types of NS.[2] Given that VTE in NS confers increased morbidity and mortality, a blood coagulation test that can detect hypercoagulable states prior to thrombosis would be ideal. TEG monitors viscoelastic changes occurring in a coagulating sample of blood, not only revealing the information about enzymes of coagulation and the kinetics of clot formation, stability and degradation but also the quantity and quality of platelets.[3] Previous studies have demonstrated that TEG exhibits strong capability to detect the hypercoagulable states in conditions, including pregnancy and postoperation.[5–8]

In this study, we assessed the utility of TEG in NS patients of various pathological types and the results showed that IMN patients had a higher hypercoagulability state compared with MCD and FSGS, which is independent of age, gender, proteinuria or serum albumin level at the time when TEG was performed. This is in line with Barbour and his colleagues's study which showed that IMN (compared to FSGS and IgA nephropathy [IgAN]) may be an independent risk for VTE after adjustment for gender, the degree of proteinuria, serum albumin levels, and cancer history.[13] R-time evaluates the intrinsic pathway and reflects the activity of coagulation factors VIII, IX, XI and XII. K-time and α-angle represent the dynamics of fibrin build-up and cross-linking. MA mainly represents platelet function. LOA4 The TEG profile of IMN demonstrated a hypercoagulable state as demonstrated by shortened K-time and increased α-angle, MA and CI values compared with MCD and FSGS. Thus, our findings suggested that platelet hyperreactivity and accelerated fibrin-platelet interaction may attribute to hypercoagulability in IMN patients. The only other study that compared TEG parameters among NS pathological types showed that by adjusting the serum albumin level, IMN had higher α-angle, MA and CI values but lower R-time than MCD.[12] The other influencing factors such as the degree of proteinuria were not tested in this study. The disease-specific risk for hypercoagulability in NS with IMN may lie in the loss of proteins of particular molecular weight, typical type of immunological injuries of nephropathies, or factor V Leiden mutation in the patients.[14–16] No difference of TEG profiles was found between MCD and FSGS, indicating that there is no difference between the coagulation disorders caused by MCD and FSGS, respectively.

In this study, there were observed differences in the incidence of VTE between IMN, FSGS, and MCD (10.4% versus 1.5% versus 2.6%). Barbour et al reported the incidence of VTE in NS patients with IMN, FSGS, and IgAN of 7.9%, 3.0% and 0.4%, respectively, using the data from 1,313 NS patients [13], while Llach et al found that the incidence of RVT in IMN, MCD and

FSGS was 30.0%, 20%, and 25% using data from 150 NS patients.[17] The variations of VTE incidence might have been derived from different methodologies and sample sizes used in the studies. Nevertheless, we can conclude that in IMN patients the incidences of both VTE and RVT are the highest among various types of nephropathies. This is consistent with the results of our study that IMN had a more evident prothrombotic state compared with other types of NS according to TEG profile. Paradoxically, in our study female patients of NS with IMN presented with more evident hypercoagulability as measured by TEG in contrast with their lower incidence of VTE compared with male patients. This phenomenon could be explained by male predominance in MN incidence (2:1 vs females) and more rapid progression to nephrotic syndrome compared with females.[18]

Moreover, we have demonstrated that the hypercoagulable state was exaggerated in patients with VTE compared with those without, as shown by the smaller R- and K-values and increased α-angle and CI values. This indicated accelerated enzymatic reaction and clot formation in the patients with VTE. Wilson et al performed TEG preoperatively, in the early postoperative period and at 6-week after operation in 250 patients undergoing proximal femoral neck fracture surgery, and found that patients with postoperative DVT had a significant trend of hypercoagulability as measured by TEG compared with those without DVT.[7] McCrath et al found that increased MA after surgery appears to be an independent predict factor for postoperative myocardial infarction.[6] However, they did not measure and assess the other parameters of TEG. In our study, the TEG MA values were higher in patients with VTE than those without although the difference did not reach statistical significance. The small group sizes in our study may partially explain for it. CI value was an independent risk factor for VTE. Previous studies have suggested that the pathogenesis of hypercoagulability in NS and thus VTE can be multifactorial, involving abnormalities in coagulation factors, antithrombotic factors, fibrinolitytic system and platelet activation in contrast with the hypercoagulability of myocardial infarction, which mainly involves platelet activation.[3,6] Therefore, CI which represents the overall coagulation profile may be more suitable for predicting VTE than the other TEG parameters.

Apart from CI value, hypoalbuminemia has been shown to be caplable of predicting VTE for NS patients with MN. This is in line with previous studies. Bellomo et al reported that serum albumin concentrations less than 2.5 g/dL was a significant risk factor for recurrence of VTE in NS patients (40 versus 2.7%, $P < .01$).[19] One prospective study from the Glomerular Disease Collaborative Network and the Toronto Glomerulonephritis Registry inception cohorts of 898 patients with IMN identified a threshold of albumin level < 2.8 g/dL. Serum albumin below this level confers 2.5-fold increase of risk for VTE.[20] We found that serum albumin of 2.1 g/dL allowed for identification of VTE patients with a rather good specificity of 93.49% and a less sensitive index of 43.75%; while a threshold of 2.3 (CI) resulted in a rather good sensitivity of 68.75%. This indicated that we may take both serum albumin and CI into consideration for predicating VTE such that early intervention may be carried out. The observed weak association between MA value and hypoalbuminemia in our study may partially explain hypercoagulability in IMN because of the association of hypoalbuminemia with platelet hyperaggregability.[21] Studies have also suggested that hypoalbuminemia can induce increased synthesis of fibrinogen, blood viscosity thus contributing to hypercoagulable state and VTE in NS.[3]

Debate continues regarding the prophylactic anticoagulation in patients with NS and increased risk for VTE because of lack of large and well - designed prospective studies that intend to evaluate the efficacy and safety of the treatment. Based on our results, the TEG analysis may serve as a tool to identify pro-thrombotic state, which helps decide more appropriate anti-coagulation treatment based on the types of coagulation disorders.

Several limitations in our study needs to be discussed. First of all, this study was retrospective; second, since patients were not subject to routine screening process, some patients with VTE who are asymptomatic might have been skipped, resulting in an underestimated VTE incidence; moreover, due to the rather small sample number of the patients with VTE, we had to use the TEG data generated within 7 days upon the detection of VTE by imaging, and the further measurement of TEG was not regularly performed in some patients with VTE after anticoagulation treatment. Therefore, a large, well-designed prospective study is required to assess the benefits of TEG analysis in guiding anticoagulation treatment in patients with VTE.

In conclusion, compared with the patients with MCD and FSGS, the patients with IMN have a more pronounced disease-specific hypercoagulable state and a higher incidence of VTE. The mechanism involves the accelerated initiation of clotting process, enhanced platelet-fibrinogen interaction and activated platelet function. Hypoalbuminemia and increased CI values are independent risk factors for VTE in IMN patients. Therefore, prophylactic anticoagulation and antiplatelet therapy may have clinical benefits for patients with IMN, especially in those with hypoalbuminemia and high CI value. However, further large and prospective studies are needed to assess the benefit versus risk in the prophylactic treatment by using TEG.

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