ORIGINAL RESEARCH

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Measurement of D-dimer as aid in risk evaluation of VTE in elderly patients hospitalized for acute illness: A prospective, multicenter study in China

Abstract

Purpose: Advanced age and hospitalization are associated with increasing risk of venous thromboembolic (VTE) events. The aim of this study was to investigate whether elevated D-dimer levels could predict VTE events in elderly patients hospitalized for acute illness.

Methods: 458 consecutive patients (65% men; mean age, 77 ± 7 years) who were older than 60 years, immobilized for ≥ 3 days, and hospitalized for heart failure, respiratory failure, acute ischemic stroke, or acute infectious disease without pharmacological prophylaxis or recent major surgery, were enrolled. Elevated D-dimer levels were defined as > 500 ng/ml. VTE events included symptomatic VTE within 90 days or asymptomatic deep venous thrombosis screened by compression ultrasonography at enrollment and 3-week follow-up. The association between baseline D-dimer levels and subsequent VTE events, adjusted for age, sex, ethnicity, body mass index, co-morbidities, and acute disease status, was assessed using multivariate Cox proportional hazard models.

Results: 49.1% ($n = 225$) of patients had elevated baseline D-dimer levels, and of these patients, 14.2% ($n = 32$) developed VTE during the 90-day follow-up. In contrast, only 5.6% ($n = 13$) of patients with normal D-dimer levels developed VTE. Multivariate analysis showed that patients with elevated D-dimer levels had a 3.2-fold increased risk of developing VTE (95% confidence interval, 1.5-6.5; $P = 0.002$) in comparison with patients with normal levels.

Conclusions: In elderly patients who were hospitalized for acute medical illness, elevated D-dimer levels are associated with subsequent VTE events. Our data suggest that measurement of D-dimer, a widely-performed objective test, may help clinicians address high-risk individuals for VTE.

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Manuscript submitted 18th January, 2011

Manuscript accepted 25th February, 2011

Clin Invest Med 2011; 34 (2): E96-E104.

Venous thromboembolism (VTE) is a frequent cause of preventable illness and death in hospitalized patients. Acutely ill patients represent a large population vulnerable to the development of VTE during hospitalization [1]. Hospitalization for acute illness is independently associated with an eight-fold increased risk for VTE [2] and accounts for almost one quarter of all VTE events [3]. The incidence of VTE increases sharply with age [4,5] and the burden of VTE is expected to grow dramatically as the population ages [6]. Simultaneously, bleeding occurs in the majority of patients with critical illness [7]. Thus, there is a need for early and reliable assessment of risk for VTE to enable appropriate triage of affected patients and to optimize outcome. Assessing the overall risk of VTE in the elderly patient hospitalized for acute medical illness is complicated, as many patients carry more than one risk factor and the effect of these risk factors tends to be multiplicative rather than additive [8]. In this context, having a marker of coagulation activation would be useful in identifying patients at high risk for VTE who might benefit from pharmacological thromboprophylaxis.

D-dimer levels is the most frequently used biomarker of coagulation and fibrinolysis activation. Elevated D-dimer can be present in those who are forming and degrading fibrin at abnormally high rates, even without evidence of a clinically significant clot. D-dimer levels have increasingly been studied as markers of coagulation activation in several clinical scenarios [9-11]. Emerging evidence endorses a 'predictive' role of elevated D-dimer levels for future VTE events in other medical conditions (eg. cancer, prior VTE) [12-14]. Nevertheless, data on the association between D-dimer levels and VTE events in elderly patients hospitalized for acute medical illness are not yet available. We hypothesized that elevated baseline D-dimer levels could serve as a biomarker for predicting VTE events in this patient population.

Subjects and Methods

Study Design

The study conformed to the principles of the Declaration of Helsinki. The study protocol was approved by the local Institutional Review Board of each participating site. All subjects provided written informed consent. Data used for analyses came from a multicenter, prospective study designed for investigating the prevalence of VTE in elderly patients hospitalized for acute medical illness.

Clinical Settings

Recruitment was conducted at 41 medical centers throughout China (see Acknowledgements for complete investigator listing). Participants were recruited between June 2006 and December 2007.

Patients

Eligible patients were 60 years of age or older; immobilized (total bed rest with bathroom privileges) for at least three days; had one or more of the following medical conditions at enrollment as documented by a staff physician: acute heart failure, chronic congestive heart failure (New York Heart Association class III or IV), respiratory failure, acute ischemic stroke or acute infectious disease.

Exclusion criteria were as follows: taking anticoagulant or thrombolytic drug at enrollment, recent major surgery (within two months prior to enrollment), evidence of clinically significant disseminated intravascular coagulation, refusal to give blood sample or participate in the study or if follow-up was deemed to be impossible.

Participants were identified consecutively from patients who were eligible in each center. If a patient was admitted to the hospital more than once during the study period, only data of their initial hospitalization was collected.

Baseline information, including birth date, sex, ethnicity, blood pressure, weight, and height, were recorded. Body mass index was calculated by dividing each patient's weight by the height squared (kg/m^2).

Information on comorbid diseases and potential VTE risk factors such as prior history of VTE, hypertension, dyslipidemia, chronic atrial fibrillation, diabetes, cancer and chronic renal failure was obtained during a standardized interview. The diagnosis of hypertension was established either with two blood pressure readings of $\geq 140/90$ mmHg or a prior diagnosis of hypertension and current treatment with antihypertensive medications. Similarly, diabetes was diagnosed if the subject had a fasting glucose measurement of > 126 mg/dl, or a random glucose of > 200 mg/dl, or had a prior diagnosis of diabetes and was on treatment with oral hypoglycemic agent(s) or insulin. Dyslipidemia was defined as total cholesterol > 200 mg/dl, or use of a lipid-lowering medication.

D-dimer Measurements

Blood was drawn at enrollment by venipuncture after an overnight fast. D-dimer plasma concentrations measurement were performed by using the STA Liatest D-dimer assay kit (Diagnostica Stago, Asnieres, France) and elevated D-dimer levels

were defined as >500 ng/ml. Laboratory technologists performing the D-dimer assays were unaware of patients' clinical presentation or the results of other objective tests.

Endpoints

Endpoints were objectively-verified VTE events, defined as pulmonary embolism (PE) and/or deep venous thrombosis (DVT), within 90 days follow-up. PE was defined as thrombus at the segmental level detected by multidetector CT angiography or magnetic resonance imaging, or in high-probability cases using planar ventilation/perfusion lung scanning, or at autopsy. Any symptomatic/asymptomatic DVT (proximal or distal) were included in the final analysis. Patients were screened for asymptomatic DVT by lower limb colour duplex ultrasonography at baseline and 3-week follow-up. The decision to evaluate a patient for other VTE events was left to the discretion of the clinician. Radiologists interpreting these studies were blinded to the patient's D-dimer levels.

Colour Duplex Ultrasonography Examination

The common femoral, deep femoral, femoral, popliteal, posterior tibial, peroneal, gastrocnemius, and soleus veins were scanned in the transverse and longitudinal plane. Duplex criteria for a diagnosis of acute DVT included visualization of thrombus on B-mode, lack of venous compressibility and the absence of Doppler flow signals distal to the site of suspected thrombosis.

Follow-up

All patients were followed up prospectively for 90 days with scheduled visits at three weeks and 90 days after enrollment. Details of any objectively confirmed VTE episode occurred during follow-up period were recorded. Discharged patients were instructed to return for reevaluation if they developed signs or symptoms suggestive of VTE.

Statistical Analysis

Continuous variables were presented as mean $\pm$ standard deviation and categorical data as numbers and percentages (%). The D-dimer data were reported as the frequency of elevated values and their comparisons were of dichotomized results (elevated *vs.* normal). Cox proportional hazards analysis was performed to evaluate the independent contribution of elevated D-dimer levels to the risk of VTE event. Initially, hazard ratios and their confidence intervals were estimated in a univariate model. Variable selection in multivariable modeling was

based on clinical and statistical significance. Significant variables from the univariate analysis, together with age, sex, ethnicity, body mass index, D-dimer, and other potential risk factors, were then subjected to multivariate Cox proportional hazard models. Kaplan-Meier survival curves were constructed and stratified according to D-dimer levels (elevated *vs.* normal) and comparisons were performed using the log-rank test. All analyses were performed with SAS9.1 (SAS Institute, Cary, N.C., USA) and a two-sided P-value of < 0.05 was deemed statistically significant.

Results

Patients

A total of 626 patients were recruited. Data from 168 patients (27%) were excluded (12 because of anticoagulant therapy at enrollment, 96 because of acute coronary syndrome requiring treatment with anticoagulation, 41 because of unwilling to give a blood sample, and 19 because of incomplete data). Thus, 458 patients were available for analysis. Follow-up was available for all of these patients.

The mean ($\pm$ standard deviation) age of participants was 77 ± 7 years, 65% were men ($n = 299$), 98% were Han ethnicity ($n = 450$), and the mean body mass index was 24.8 ± 4.3 kg/m². Reasons for enrollment were heart failure ($n = 247$, 54%), respiratory failure ($n = 28$, 6%), acute ischemic stroke ($n = 65$, 14%), or acute infectious disease ($n = 146$, 32%). The prevalence of hypertension and diabetes in this cohort was 38% ($n = 176$) and 35% ($n = 159$), respectively. A total of 61% had experienced coronary heart disease/cerebrovascular disease ($n = 281$), and 4% had experienced VTE event(s) previously ($n = 17$). Regarding mechanical thromboprophylaxis, only 0.4% ($n = 2$) of the patients had used graduated compression stockings and none had used intermittent pneumatic compression.

The main demographic and clinical characteristics of the patients are detailed in Table 1. The patients were divided into two groups, based on D-dimer levels, and these two groups did not differ in demographic variables. Compared with those who had normal baseline D-dimer levels, patients with elevated baseline D-dimer levels had a higher prevalence of heart failure (59.1% *vs.* 48.9%; $P = 0.029$), chronic renal failure (8.9% *vs.* 3.8%; $P = 0.027$) and lower prevalence of hypertension (33.8% *vs.* 42.9%; $P = 0.044$). In the subgroup of patients with elevated baseline D-dimer levels (Table 2), the prevalence of heart failure (62.7% *vs.* 37.5%; $P = 0.007$) and cardiovascular/cerebrovascular disease (62.2% *vs.* 43.7%; $P = 0.049$) were significantly higher in patients without VTE events compared

TABLE 1. Baseline Clinical Characteristics of Study Participants, Grouped According to D-dimer Levels

	Patients with normal baseline D-dimer levels (n = 233)	Patients with elevated baseline D-dimer levels (n = 225)	P Value
Demographic Factors			
Age (years)	76.9 ± 7.5	77.2 ± 7.7	0.363
Ethnicity (Han)	230 (98.7%)	220 (97.7%)	0.445
Sex (Male)	156 (66.9%)	143 (63.5%)	0.445
Body Mass Index (kg/m ²)	24.7 ± 4.2	24.9 ± 4.5	0.221
Reason for Hospitalization			
Heart failure	114 (48.9%)	133 (59.1%)	0.029
Respiratory failure	11 (4.7%)	17 (7.5%)	0.206
Acute ischemic stroke	42 (18.0%)	23 (10.2%)	0.017
Acute infectious diseases	70 (30.0%)	76 (33.8%)	0.391
Co-morbidities			
CAD/CVD	147 (63.1%)	134 (59.6%)	0.437
Hypertension	100 (42.9%)	76 (33.8%)	0.044
Diabetes	159 (35%)	73 (32.4%)	0.316
COPD	35 (15.0%)	38 (16.9%)	0.585
Chronic atrial fibrillation	14 (6.0%)	21 (9.3%)	0.181
Dyslipidemia	23 (9.9%)	16 (7.1%)	0.290
Chronic renal failure	9 (3.8%)	20 (8.9%)	0.027
Tumor	14 (6.0%)	15 (6.7%)	0.773
Prior VTE	5 (2.1%)	12 (5.3%)	0.071
Follow-up			
VTE events	13 (5.6%)	32 (14.2%)	0.002
Deaths	14 (6.0%)	25 (11.1%)	0.050

N=458. Continuous variables are presented as mean ± standard deviation and categorical data as numbers and percentages (%). CAD=coronary artery disease, CVD=cerebrovascular disease, COPD=chronic obstructive pulmonary disease, VTE=venous thromboembolism.

with those with VTE events. Conversely, the rate of respiratory failure (5.7% vs. 18.7%; $P = 0.010$) was relatively lower.

D-dimer and VTE events

Of the total 458 patients, 49.1% (n = 225) had elevated baseline D-dimer levels. During the 90-day follow-up, 45 participants (9.8%) had at least one VTE event, including fifteen (3.3%) asymptomatic/silent DVT cases screened by lower limb colour duplex ultrasonography. There were 32 (14.2%) cases of VTE in patients with elevated baseline D-dimer levels, as compared with 13 (5.6%) in those with normal levels (Table 1). The outcomes of patients with asymptomatic/silent DVT were relatively benign: none developed PE and only 1 (6.7%) died during the 90-day follow-up. The Kaplan-Meier VTE-free survival curves (Figure 1) show that an elevated D-dimer level was predictive of VTE during the 90-day follow-up ($P = 0.002$ by the Log-Rank test).

FIGURE 1. Kaplan-Meier estimate of venous thromboembolic event-free survival comparing patients with and without elevated D-dimer levels at baseline (Log Rank test $P=0.002$)

TABLE 2. Clinical Characteristics of Subgroup of Patients with Elevated Baseline D-dimer Levels, According to Outcomes

	Patients without VTE (n = 193)	Patients with VTE (n = 32)	P Value
Demographic Factors			
Age (years)	77.1 ± 7.5	78.3 ± 9.1	0.111
Ethnicity (Han)	189 (97.9%)	31 (96.8%)	0.708
Sex (Male)	125 (64.7%)	18 (56.3%)	0.354
Body Mass Index (kg/m ²)	24.9 ± 4.5	25.2 ± 4.4	0.788
Reason for Hospitalization			
Heart failure	121 (62.7%)	12 (37.5%)	0.007
Respiratory failure	11 (5.7%)	6 (18.7%)	0.010
Acute ischemic stroke	18 (9.3%)	5 (15.6%)	0.276
Acute infectious diseases	61 (31.6%)	15 (46.8%)	0.091
Co-morbidities			
CAD/CVD	120 (62.2%)	14 (43.7%)	0.049
Hypertension	69 (35.7%)	7 (21.8%)	0.124
Diabetes	64 (33.2%)	9 (28.1%)	0.573
COPD	29 (15.0%)	9 (28.1%)	0.067
Chronic atrial fibrillation	20 (10.4%)	1 (3.1%)	0.192
Dyslipidemia	13 (6.7%)	3 (9.4%)	0.591
Chronic renal failure	19 (9.8%)	1 (3.1%)	0.216
Tumor	14 (7.3%)	1 (3.1%)	0.386
Prior VTE	10 (5.2%)	2 (6.3%)	0.803
Follow-up			
Deaths	20 (10.4%)	5 (15.6%)	0.380

N=458. Continuous variables are presented as mean ± standard deviation and categorical data as numbers and percentages (%). CAD=coronary artery disease, CVD=cerebrovascular disease, COPD=chronic obstructive pulmonary disease, VTE=venous thromboembolism.

Cox Proportional Hazards Models

On univariate Cox regression analysis, there was a 2.3-fold increased risk of VTE among patients with elevated D-dimer levels compared with patients with normal D-dimer levels (hazard ratios 2.30; 95% confidence intervals 1.18-4.45; $P = 0.014$, Table 3). In addition, respiratory failure ($P = 0.011$), infectious disease ($P = 0.033$) and prior VTE ($P = 0.029$) were also associated with VTE events. Elevated D-dimer levels was an independent predictor of VTE after adjustment for demographic factors and body mass index (hazard ratios 2.6; 95% confidence intervals 1.4-5.0; $P = 0.004$; Table 4) and for potential confounding factors including presence of infectious disease, heart failure, respiratory failure, prior VTE, coronary artery disease/cerebrovascular disease, chronic atrial fibrillation, cancer, chronic obstructive pulmonary disease, chronic renal failure, diabetes, tumor, hypertension and mechanical thromboprophylaxis (hazard ratios 3.2; 95% confidence intervals 1.5-6.5; $P = 0.002$; Table 4).

Discussion

The main finding of this multicenter prospective study was that elevated D-dimer levels at baseline identified high risk for VTE in elderly patients hospitalized for acute medical illness. 14.2% of them developed VTE during 90-day follow-up. By contrast, only 5.6% developed VTE in the cohort with normal D-dimer level. These data indicate that activation of the coagulation system is an important pathophysiologic indicator of occurrence of VTE and the measurement of D-dimer in elderly patients hospitalized for acute medical illness is a valuable tool for identification of patients prone to develop VTE.

This is the first study to demonstrate that elevated D-dimer levels have independent predictive value for the subsequent VTE events in elderly patients hospitalized for acute illness. The patients studied here reflect those usually encountered in clinical practice: they are older than those included in large clinical trials of thromboprophylaxis, in which subjects over 75 years were excluded, and have multiple comorbid con-

TABLE 3. Univariate Cox Proportional Hazard Analysis of Relationship Between Potential Risk Factors and Subsequent VTE Events

	Hazard Ratio (95% Confidence Interval)	P Value
Demographic Factors		
Age	1.03 (0.98-1.07)	0.240
Sex (Male)	0.92 (0.48-1.79)	0.815
Body mass index	0.97 (0.90-1.04)	0.423
Reason for Hospitalization		
Infectious disease	1.97 (1.06-3.66)	0.033
Heart failure	0.55 (0.29-1.04)	0.065
Respiratory failure	3.06 (1.29-7.30)	0.011
Acute ischemic stroke	1.30 (0.58-2.94)	0.527
Co-morbidities		
CAD/CVD	0.55 (0.29-1.01)	0.055
Hypertension	0.60 (0.30-1.19)	0.144
Chronic atrial fibrillation	0.64 (0.15-2.65)	0.537
Diabetes	0.99 (0.52-1.90)	0.980
Chronic obstructive pulmonary disease	0.12 (0.87-3.62)	0.118
Chronic renal failure	0.77 (0.19-3.20)	0.721
Dyslipidemia	0.75 (0.42-3.32)	0.751
Tumor	0.37 (0.05-2.70)	0.327
Prior VTE episode(s)	3.16 (1.13-8.89)	0.029
D-dimer Measurement		
Baseline D-Dimer levels (elevated)	2.30 (1.18-4.45)	0.014

VTE=venous thromboembolism; CAD=coronary artery disease; CVD=cerebrovascular disease.

TABLE 4. Associations of Baseline D-Dimer Levels with Subsequent VTE events: Multivariate Cox Proportional Hazard Models*

	Hazard Ratio (95% Confidence Interval)		P Value
	Normal D-dimer levels (referent group)	Elevated D-dimer levels	
Unadjusted	1	2.7 (1.4-5.1)	0.003
Model 1	1	2.6 (1.4-5.0)	0.004
Model 2	1	3.2 (1.5-6.5)	0.002

* n=458

Model 1: Hazard ratio adjusted for age, sex, ethnicity, and body mass index;

Model 2: Hazard ratio adjusted for variables in model 1 plus infectious disease, heart failure, respiratory failure, prior venous thromboembolic event(s), coronary artery disease/cerebrovascular disease, chronic atrial fibrillation, chronic obstructive pulmonary disease, chronic renal failure, diabetes, tumor, hypertension, and mechanical thromboprophylaxis.

ditions. Given the fact that this study included only patients without pharmacological thromboprophylaxis and that 0.4% of the study population used mechanical prophylaxis, we believe that results of this study reflect the natural history of the population of this age.

These results are consistent with previous observations for the role of D-dimer levels in the prediction of initial or recurrent VTE in other patients with other medical conditions [10, 12, 15-17]. Most importantly, in the present study, the prevalence of VTE in elderly patients hospitalized for acute illness

who were also found to have elevated D-dimer levels is 14.2% - much higher than that previously reported in similar patients without consideration of D-dimer levels (3.4 ~ 6.6%) [18-20]. The potential value of D-dimer levels as a predictor of VTE in elderly patients hospitalized for acute illness lies in the possibility of pharmacological intervention within a period when the risk of VTE is higher than normal. Selecting patients at highest risk means that antithrombotic prophylaxis can be reserved for those promising the best ratio between likely benefit and risk of

bleeding. Validation of our results in a large population would provide more precise estimates of the risk for VTE.

The pathophysiological mechanisms leading to the development of VTE and elevated D-dimer levels in elderly patients hospitalized for acute illness remains to be clarified. D-dimer is formed by the action of plasmin fibrin clot and generated in the presence of thrombus [21,22]. D-dimer represents the summation of procoagulant balance, genetic factors or the presence of underlying coagulation disorders that predispose to VTE. Many of the clinical factors in this setting, such as old age, congestive heart failure, respiratory failure, ischemic stroke, infectious disease, inflammatory disorders and bed rest, will affect the balance of thrombosis and fibrinolysis activation. The elevated levels of D-dimer may reflect any one of several underlying disease processes that initiate intravascular fibrin formation and provide a detectable warning sign of hypercoagulability and increased risk of thrombosis. A normal D-dimer level denotes no major ongoing activation of intravascular coagulation. It must be stressed that the balance of coagulation and fibrinolysis in the human body changes with disease progression or regression. Repeated D-dimer assays in patients with an originally normal test may be useful in detecting a late hypercoagulability. Much more work needs to be done to determine whether dynamic monitoring of D-dimer levels might provide additional information and might be useful for continuous VTE risk evaluation for elderly patients hospitalized for acute illness.

Interestingly, some typical risk factors for VTE, such as tumor, age and body mass index, were not statistically significant in the univariate analysis of our study (Table 3). The likely explanation is only elderly patients (mean age 77 yrs) were enrolled in the study and that the prevalence of patients with cancer ($n = 29$, 6.3%) or obesity (mean BMI 24.8 ± 4.3 kg/m²) was relatively low in this study. Thus, it is difficult to draw conclusion on the relationship among these factors and VTE.

Our study had several methodological strengths. The main strength is its prospective design with screening of consecutive eligible patients and use of a standardized data collection. Data were rarely missing. Another strength was that diagnosis and management of patients was determined by the treating physicians, and hence the data reflect a real-world approach to these patients; patients included both sexes and represented a broad spectrum of clinical characteristics. Moreover, we included asymptomatic DVT cases confirmed by colour duplex ultrasonography without exposing our fragile patients to an invasive procedure.

Even so, however, a few points should be considered in interpreting these findings. First, this study focused especially

on elderly inpatients hospitalized for acute illness without pharmacological thromboprophylaxis, the applicability of our findings to other patients requires further study. Second, it is possible that our data on comorbidity or other clinical factors were insufficient to allow us to fully adjust for potentially confounded effects. Finally, only clinically identified VTE events were included. While all patients were followed for 90 days, silent or non-clinically evident VTE complications could have occurred.

Conclusions

Our study shows that elevated baseline D-dimer levels are associated with subsequent VTE events in elderly patients hospitalized for acute medical illness. The strength of the association observed here suggests that the measurement of D-dimer levels in plasma has a definite place in the procedure for identifying high-risk VTE patients.

Acknowledgments

We thank Iftikhar J. Kullo, MD, (Cardiovascular Division, Department of Internal Medicine, Mayo Clinic) for his insightful comments on this work. We are grateful to Sainan Zhu (Peking University First Hospital) for preliminary analyses. We thank Yan Wang who was responsible for administration of the follow-up data and who supported us in data base administration, and the Vascular Ultrasound Core Laboratory of Chinese PLA General Hospital for their technical support. Declaration of conflict of interest: Dr. Xiaoying Li received research support from Pfizer and GlaxoSmithKline. None of the other authors declare any conflicts of interest.

We thank all persons that supported us in patient recruitment and follow-up for the present study. In addition to the cited authors, the Investigators also include: Beijing: Ying Yuan, MD, Beijing Mei Tan General Hospital; Weixing Lu, MD, Beijing Dong Zhi Men Hospital; Huiji Wang, MD, Beijing Friendship Hospital; Yujie Zhou, MD, Beijing An Zhen Hospital; Yunfeng Xia, MD, 304 Hospital of PLA; Ruijie Li, MD, Beijing Chui Yang Liu Hospital; Yuanhui Hu, MD, Beijing Guang An Men Hospital; Mingsheng Wang, MD, Beijing Shi Jing Shan Hospital; Haiyan Li, MD, Beijing He Ping Li Hospital; Guogan Wang, MD, Beijing Fu Wai Hospital; Jianguo Wu, MD, Beijing Hai Dian Hospital; Zechang Xu, MD, Beijing Jian Gong Hospital; Bin Wang, MD, Beijing Hang Tian Hospital, Peking University; MingZhao Qin, MD, Beijing Tong Ren Hospital; Zhigang Zheng, MD, China-Japan Friendship Hospital; Kalin Chu, MD, Beijing Ji Shui Tan Hospital; Meilin Liu, MD, Peking University First Hospital;

Fuchun Zhang, MD, Peking University Third Hospital; Lin Zhang, MD, Beijing Chao Yang Hospital; Xiaoping Xiang, MD, Beijing Sixth Municipal Hospital; Yide Miao, MD, Peking University People's Hospital; Xichao Guo, MD, Beijing Wu Jing Hospital; Qing He, MD, Beijing Hospital; Pu Feng, MD, Yuquan Hospital of Tsinghua University; Jianchang Wang, MD, Air Force General Hospital; Yin Han, MD, General Hospital of Armed Police Forces; Yang Wu, MD, Beijing University of Chinese Medicine and Pharmacology Dong Fang Hospital; Xiaofa Zhu, MD, Navy General Hospital; Hongxu Liu, MD, Beijing Hospital of Traditional Chinese Medicine; Fenghe Du, MD, Beijing Tian Tan Hospital; Buxing Chen, MD, Beijing Dian Li Hospital. Shandong Province: Zishan Hou, MD, Linyi Municipal Hospital; Haiqing Gao, MD, Qi Lu Hospital of Shandong University; Jianchun Wang, MD, Shandong Provincial Hospital; Shanxi Province: Ruxiang Li, MD, Third Hospital of Shanxi Medical University; Zhilan Li, MD, 264 Hospital of PLA; Liangqing Zhang, MD, Cardiovascular Hospital of Shanxi Province; Jianing Tang, MD, Tai Gang Workers' Hospital; Weizhen Xue, MD, Taiyuan Central Hospital.

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