Plasma D-dimer levels are correlated with disease severity among hypertensive patients
A comparative cross-sectional study

Yanli Long, MDa, Yi Li, MDa, Litao Zhang, MDa, Liang Tao, MDa, Hongyan Xiao, MDa, Ying Li, MDa, Chunyou Zhou, MDc,*

Abstract

It has been reported that inappropriate acute thrombus formation is the pathophysiological substrate underlying increased risk and severity of target organ damage in hypertension (HTN). However, the relationship between severity of HTN and D-dimer has not been well characterized. The study was aimed to assess plasma D-dimer level and its correlation with disease severity among hypertensives. A comparative cross-sectional study was conducted at Wuhan Asia Heart Hospital among 100 participants (60 hypertensives and 40 controls). The correlation between variables were determined using correlation coefficients, regression analysis, and also using different parametric and nonparametric tests. We observed higher D-dimer levels among hypertensives compared to the healthy controls (P < .001). The D-dimer levels were found to be increased significantly with the severity of HTN (P < .001). D-dimer was found to have a diagnostic power of 86.9% in differentiating complicated from uncomplicated HTN at 0.83 mg/L cutoff value. This study suggests that D-dimer level was higher among hypertensives than control groups and it was also increasing significantly with the severity of HTN. This suggests that hypercoagulability of fibrin plays a role in the occurrence of thromboembolic complications of hypertensive patients.

Abbreviations: AUC = area under the curve, BMI = body mass index, BP = blood pressure, CHD = coronary heart disease, CI = confidence interval, CVD = cardiovascular disease, DBP = diastolic blood pressure, D-DI = D-dimer, HTN = hypertension, PAD = peripheral arterial disease, ROC = receiver operating characteristic, SBP = systolic blood pressure, TOD = target organ damage.

Key words: D-dimer, disease severity, hypertension, thromboembolic complications.

1. Introduction

Hypertension (HTN) is the most important modifiable cardiovascular risk factor that, in long-term, leads to target organ damage (TOD) or thromboembolic complications associated with heart, brain, kidney, and peripheral arteries, resulting increased morbidity and mortality.[1,2] HTN doubles the risk of stroke, coronary heart disease, peripheral arterial disease (PAD), and end-stage renal disease. A plethora of studies have examined that essential HTN, independently or by clustering with the coexisting risk factors such as age, gender, smoking, obesity, diabetes, and dyslipidemia, is involved in the development of TOD[3]; with complications predominantly occurring as a result of thrombotic rather than hemorrhagic factors.[4,5]

The risk of cardiovascular disease resulting from hypercoagulability, due to endothelial injury in hypertensive disorder can be proven by measuring D-dimer (D-DI) level which is more sensitive, highly predictive and noninvasive procedure though it has little specificity and low positive predictive value (PPV).[6] D-DI is reportedly a good independent biochemical risk marker of thrombogenesis and fibrin turnover.[7] In patients without evidence of coagulopathy, the D-DI may represent microvascular thrombosis and the elevated levels of which may provide clinical utility in predicting risk of future myocardial infarction, stroke, and PAD in the general population.[8,9]

Although the relationship between HTN and D-DI level has been reported previously and gained great interest among researchers worldwide in recent years, to the best of our knowledge, studies addressing the severity of HTN and D-DI level are rare worldwide. Therefore, this study was undertaken primarily to assess D-dimer level and its correlation with disease severity among hypertensive patients. Specifically, we sought to compare D-dimer level in hypertensive patients with apparently healthy individuals and also to evaluate the correlation between plasma D-dimer level and the severity of HTN.

Besides, we aimed to determine predictive ability of plasma D-dimer to differentiate between complicated and uncomplicated HTN.
2. Methods

2.1. Study area, design, and period

A comparative cross-sectional study was designed and conducted in Wuhan Asia Heart Hospital in Wuhan, China from May 3 to June 9, 2019.

2.2. Population

Plasma D-Dimer level was measured in 60 hypertensive patients attending our institution and 40 volunteer healthy individuals during the study period using purposeful sampling technique. But, study participants with suspected deep venous thrombosis, pulmonary embolism, disseminated intravascular coagulation, recent surgery/trauma (in the last 3 months), pregnancy, early age (<20 year), and advanced age (>80 year), known history of diabetes mellitus, renal failure, or liver disease, those on anticoagulatory (heparin or warfarin) or thrombolytic treatment (streptokinase or urokinase) were excluded from the study by reviewing patient’s card and historically from the participants as well as through interview. The protocol was approved by the Ethics Committee of Wuhan Asia Heart Hospital.

2.3. Study variables

Plasma D-Dimer level was dependent (criterion) variable while socio demographic factors (age, sex, marital status, residence, occupation, education); behavioral factors (smoking, alcohol use, physical activity); family history of HTN; anthropometric parameter (body mass index [BMI], weight, height); and clinical factors like BP, weight, and height. BP was measured in the morning (before taking antihypertensive drug) at sitting positions from right arm in a quiet room using an Omron automatic device after making patient comfortable and after 15 minutes of rest. A mean of 2 measurements (taken at different occasion) was used to determine systolic blood pressure (SBP) and diastolic blood pressure (DBP) in each participant. Hypertension was defined based on World Health Organization criteria, SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or reported regular use of antihypertensive drug. Since BP measurements alone while on antihypertensive regimen have been considered a less reliable indicator of HTN severity, the combination of BP levels, number of drugs taken (not fixed drug combinations), and presence of complication were used to indicate the disease severity of adult hypertensives (aged>20 years) and were divided into 3 clinical stages; stage 1 HTN if BP was 140/90–159/99 or taking 1 or 2 antihypertensive medications; stage 2 HTN if BP > 160/100, or taking 3 or more medications and severe HTN if BP > 180/120 or complication present. The study comparatively analyzed D-Di level between normotension and HTN as well as between stage 1, stage 2, and severe HTN. “Complicated” HTN is defined as the patient has thromboembolic complication (like stroke, heart disease [myocardial infarction, left ventricular hypertrophy, cardiac arrhythmia, or CAD], secondary renal failure, PAD) developed as a result of HTN. The weight of the participants was measured using a standard balance, while the height was measured using a height measuring scale with light clothing and without shoes. BMI was then calculated based on the formula: BMI = Weight (in kg)/(Height in m^2). Using the De Lorenzo et al classification, 4 categories of BMI were identified: underweight, <18.5 kg/m^2; normal, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; and obese, >30 kg/m^2.

2.4. Data collection

After informed consent, sociodemographic data, medical data, and risk factors were collected from the selected participants using structured questionnaire through face to face interview, reviewing patient’s card and direct measurement of the variables like BP, weight, and height. BP was measured in the morning (before taking antihypertensive drug) at sitting positions from right arm in a quiet room using an Omron automatic device after making patient comfortable and after 15 minutes of rest. A mean of 2 measurements (taken at different occasion) was used to determine systolic blood pressure (SBP) and diastolic blood pressure (DBP) in each participant. Hypertension was defined based on World Health Organization criteria, SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or reported regular use of antihypertensive drug. Since BP measurements alone while on antihypertensive regimen have been considered a less reliable indicator of HTN severity, the combination of BP levels, number of drugs taken (not fixed drug combinations), and presence of complication were used to indicate the disease severity of adult hypertensives (aged>20 years) and were divided into 3 clinical stages; stage 1 HTN if BP was 140/90–159/99 or taking 1 or 2 antihypertensive medications; stage 2 HTN if BP > 160/100, or taking 3 or more medications and severe HTN if BP > 180/120 or complication present. The study comparatively analyzed D-Di level between normotension and HTN as well as between stage 1, stage 2, and severe HTN. “Complicated” HTN is defined as the patient has thromboembolic complication (like stroke, heart disease [myocardial infarction, left ventricular hypertrophy, cardiac arrhythmia, or CAD], secondary renal failure, PAD) developed as a result of HTN. The weight of the participants was measured using a standard balance, while the height was measured using a height measuring scale with light clothing and without shoes. BMI was then calculated based on the formula: BMI = Weight (in kg)/(Height in m^2). Using the De Lorenzo et al classification, 4 categories of BMI were identified: underweight, <18.5 kg/m^2; normal, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; and obese, >30 kg/m^2.

2.5. Sample collection and analysis

After informed consent, 4 mL of venous blood was drawn from each participant via venipuncture from the antecubital vein and was poured into ethylene diamine tetraacetic acid tube. After it was thoroughly mixed with the anticoagulant inside the tube, blood was centrifuged for 15 minutes at 3000 rpm within 4 hours after collection at room temperature to obtain plateletpoor plasma. Plasma was separated from cells into Nunc tube using micropipette and then platelet-poor plasma was stored and refrigerated at −20°C until assayed. One ml plasma was taken into sample tube for analysis and plasma D-dimer was measured by fully automated immunoturbidimetric assay, using a Roche COBAS INTEGRA 6000 analyzer using the Tina-quant D-dimer Gen.2 test. The Tina-quant D-dimer test was then performed using a cutoff of 0.5 mg FEU/L.

2.6. Data collection and analysis

Data was statistically analyzed using SPSS version 25.0. Independent samples t-test and Wilcoxon Mann Whitney U tests were used to see the difference in the mean values of continuous variable between hypertensive and control groups as well as between study variables with 2 responses accordingly. One-way analysis of variance (ANOVA) and Kruskal-Wallis tests were also used to see the difference in the mean values of D-dimer level among the 3 stages of HTN and other study variables with 3 or more responses. The correlation between continuous variables that met the assumptions were computed using the Pearson correlation coefficient. A point-biserial correlation coefficient was used for the dichotomous variables. Correlations between the ordinal variables and continuous variables that don’t meet the normality assumptions were assessed by Spearman nonparametric test. Simple and multivariate regression analyses were performed to examine the predictive variables and odds ratio. Adjusted odds ratio with 95% confidence interval (CI) was used to show the strength of association. Those variables with a 2-sided P-values of <.05 were considered as statistically significant. The diagnostic or predictive performance of D-dimer levels for HTN related complications was evaluated using a receiver operating characteristic (ROC) curves analysis.

3. Result

3.1. D-dimer levels were significantly elevated in hypertensive patients

The concentrations of D-Dimer (D-DI) exceeded the normal range (>0.5 mg/L FEU) in 38 (63.3%) of hypertensives and 8 (20.0%) of controls. From independent sample t-test, it was observed that a significantly higher (P < .001) mean value of D-DI levels among hypertensives (1.1 ± 2.0 mg/L) compared to control groups (0.37 ± 0.3 mg/L) (Table 1).

3.2. Comparison of d-DI levels between different independent variables

Independent sample t-test (Table 2) showed that there was statistically significant higher mean levels of plasma D-DI (P < .05) in poorly controlled hypertensives compared to the well-controlled hypertensive patients. In addition, results showed that complicated hypertensives had significantly elevated plasma D-DI level than uncomplicated patients (P < .001).

One-way ANOVA showed there were statistically significant differences in mean plasma D-DI level (P < .05) among different groups of age, BMI, BP and number of antihypertensive drugs (Table 3 and Fig. 1).
3.3. Comparison of d-DI levels according to the severity of hypertension

Plasma D-DI levels were increased significantly with the severity of HTN \( (P < .001) \), in which the mean D-DI level of severe HTN \( (1.6 \pm 0.87 \text{ mg FEU/L}) \) were significantly higher compared to both stage 1 HTN \( (0.50 \pm 0.25 \text{ mg FEU/L}) \) and stage 2 HTN \( (0.99 \pm 0.63 \text{ mg FEU/L}) \) from 1-way ANOVA (Table 4 and Fig. 2).

The Tukey HSD post hoc analysis showed that there was statistically significant difference \( (P < .05) \) in mean plasma D-DI level in any of pair combinations among the clinical stages of HTN i.e. between stage 1 HTN versus stage 2 HTN and...
severe HTN as well as between stage 2 HTN and severe HTN (Table 5).

3.4. Correlation and regression analysis of d-DI level with independent variables

Among hypertensive patients, age (r = 0.285, P = .004), BMI (r = 0.214, P = .032), SBP (r = 0.312, P = .002), DBP (r = 0.221, P = .027), presence of complication (r = 0.57, P < .001), and severity of HTN (ρ = 0.66, P < .001) were found to have statistically significant positive correlation with D-DI values. The mean plasma D-DI level was increased with age, SBP (Fig. 3), severity of HTN, and DBP. In contrary, the number of antihypertensive drugs (r = −0.238, P = .007) and BP control status (r = −0.804, P = .033) were negatively correlated with D-DI levels. However, no significant correlations existed between D-DI values and sex, smoking status, alcohol consumption, physical activity, family history of HTN or duration of HTN.
As illustrated in Table 6, after adjusting for the effects of other variables, SBP, severity of HTN, presence of complication and BP control status were found to have independently significant association with plasma D-DI level. Systolic BP was found to be a significant predictor of plasma D-DI level in HTN in which 1-unit increase in SBP elevates the D-DI level by 0.001 (B = 0.001, \( P < .023 \)). It was also observed that there was a significant change in the level of plasma D-DI across the clinical stages (severity) of HTN. Accordingly, for a 1-unit increase to a higher-level clinical stage, there was an increase in D-DI level by 0.569 (\( P < .001 \)). While all other independent variables are held constant, the presence of complication, such as stroke or heart diseases, significantly increased the plasma D-DI level by factor of 1.048 (\( P < .001 \)).

### 3.5. Diagnostic performance of D-DI levels for disease severity in hypertension

The diagnostic performance of D-DI for presence of thromboembolic complication in hypertensive patients was further investigated using a ROC curve (Fig. 4). We found that the area under the curve (AUC), measuring the overall diagnostic performance of the D-DI test, was 0.869 (95% CI: 0.773–0.964) at \( P < .001 \) which indicated AUC is significantly different from 0.5.

The optimal cutoff value for the D-DI concentration (0.83 mg/L FEU) was selected based on ROC curve analysis. The amount of D-DI was determined to be an effective diagnostic marker for severe (complicated) HTN. At a cutoff value of 0.83 mg/L, the D-DI concentration had a sensitivity of 87.5%, a specificity of 77.5% with a PPV of 87.5% and negative predictive value of 77.3%. The D-DI test also had an accuracy of 80.0% (Table 7).
4. Discussion

The association between HTN and the activation of blood coagulation was elucidated in different literatures. Commonly observed in hypertensive patients, the hypercoagulable state appears to act as an important risk factor for thrombotic complications and may play a role in disease progression.[13] Among the degradation products resulting from the proteolytic actions of plasmin on fibrin, D-dimer is the smallest fibrin degradation byproduct, exhibiting unique characteristics. D-DI can be used to estimate the state of activation of the coagulation system, which is elevated by increasing fibrin formation and fibrinolysis.[9]

This study, therefore, strived to assess plasma D-DI level and its correlation with disease severity among hypertensive patients. We utilized a fully automated quantitative approach for the determination of D-DI level in 60 hypertensive patients and the values were compared with 40 unmatched normal subjects. Our data demonstrated that about 63.3% of hypertensives had excessive concentrations of plasma D-DI level. The study also indicated that plasma D-DI levels significantly increased among hypertensive patient compared to healthy controls. This finding is consistent with a number of studies that have found elevated plasma D-DI levels in essential HTN and white coat hypertension groups than in healthy controls.[14–19] A comparative cross-sectional study has also supported this finding showed that hypertensive patients tended to have an unbalanced fibrinolytic system and tendency towards a hypercoagulability and a more frequently thrombotic complications compared to normotensive subjects.[19] Finding of high fibrin D-DI in patients with HTN suggests hypercoagulable state and ongoing intravascular fibrin formation (and possibly early thrombus formation) that plays a role in the pathogenesis of cardiovascular diseases and complications of HTN. However, this finding was conflicting with another study done in Sudan and a study by Sechi et al who showed that the D-DI level was insignificantly increased in hypertensive patients when compared with healthy controls.[20,21] This discrepancy may probably be related to a difference in sample size and study design.

After adjustment of confounders, through multiple linear regression, SBP, severity of HTN, presence of complication and BP control status were found to be possible predictor variables of D-DI level though the direction of causation was poorly defined which is the inherent property of cross-sectional study design. Unlike DBP, SBP was found to be the significant predictors of plasma D-DI level in HTN in which a unit increase in SBP elevates the D-DI level by 0.001. This is partially consistent with a report which indicated that high SBP and DBP were found to be independent predictors of plasma D-DI level.[13] Poorly controlled HTN has 0.41 higher D-DI level than the well-controlled HTN suggesting controlling BP has a lowering effect on D-DI level.

The novel finding of the current study was the association of plasma D-DI with the severity of HTN in where a more severe stage of HTN has a significantly higher D-DI values than the lower stages. The finding was unchanged after the adjustment for confounding variables in which a 1 level increase to the higher stage of HTN significantly increased the plasma D-DI level by factor of 0.569. This suggests that patients with elevated plasma D-DI level have more severe HTN compared to hypertensive patients with normal D-DI level though the poor PPV of the test require supportive test to exclude other possible

### Table 6

| Variables                      | B*       | 95% CI for B | P  |
|-------------------------------|----------|--------------|----|
| Age, year                     | 0.003    | -0.010 - 0.016 | .636|
| BMI (kg/m²)                   | 0.024    | -0.008 - 0.056 | .136|
| SBP (mm Hg)                   | 0.001    | 0.000 - 0.013 | .023|
| DBP (mm Hg)                   | 0.004    | -0.019 - 0.021 | .736|
| Presence of complication      | 1.048    | 0.691 - 1.405 | <.001|
| No. of antihypertensive drugs | 0.211    | -0.015 - 0.438 | .067|
| Severity of hypertension      | 0.569    | 0.373 - 0.764 | <.001|
| BP control status             | 0.410    | 0.262 - 0.543 | .020|

*B indicates unstandardized model coefficients to indicate how much the dependent variable varies with an independent variable when all other independent variables are held constant. P-values written in bold are significant at < 0.05.

BMI, body mass index, CI = confidence intervals, DBP = diastolic blood pressure, D-DI = D-dimer level, HTN = hypertension, SBP = systolic blood pressure.

### Table 7

| Cutoff value | Sensitivity, % | Specificity, % | PPV, % | NPV, % | Accuracy, % |
|--------------|----------------|----------------|--------|--------|-------------|
| D-DI (0.83 mg/L) | 87.5           | 77.5           | 87.5   | 77.3   | 80.0        |

D-DI = D-dimer level, NPV = negative predictive value, PPV = positive predictive value.

![Figure 4. ROC curve analysis for the prediction of thromboembolic complications. AUC = area under the curve, CI = Confidence interval, ROC = receiver operating characteristic.](image-url)
causes of elevated D-DI and arrive at conclusion. This is in corri-
roboration with previous studies which showed that the level of
D-DI increased by progression of HTN to higher or more severe
stage.[15,23]

D-dimer level was significantly elevated (by a factor of 1.048)
in patients with complicated HTN, such as stroke and heart
diseases, compared with those patients without complication
while all other independent variables were held constant. These
results are consistent with findings from prior study by Chi et
al.[10] demonstrating that hypertensive patients with left ventricu-
lar hypertrophy, left ventricular enlargement, and left atrial
enlargement, were found to have higher levels of D-DI. This was
also supported by Sechi et al.[21] who reported that higher D-DI
levels were independently associated with advanced TOD in
hypertensive patients. It has been suggested that thrombus for-
mation is involved in HTN progression to complicated type as
a result of promoting vessel thrombus occlusion and embolism.
Further studies with more laboratory investigations and clinical
data are needed for logical interpretation and accurate conclu-
sion of the association of an elevated D-DI level and TOD in
hypertensive patients. This is an important finding with a benefit
for a better management of hypertensive patients.

D-dimer also predicts the presence and severity of HTN-
related damage in different organs. D-dimer is a classic marker,
which is easy and convenient to test and could be measured in
prediction of thrombotic complications associated with HTN.
The ROC curve analysis and the corresponding AUC in this
study showed that plasma D-DI as a biomarker has a predictive
ability to discriminate complicated HTN from uncomplicated
one. The level of D-DI was determined to be an effective diag-
nostic marker for thrombotic complications in HTN with an
AUC of 0.869 (95% CI: 0.773–0.964) as well as with a sen-
sitivity and a specificity of 87.5% and 77.5% respectively at
an FEU cutoff value and an accuracy rate of 80.0%. To the best
of our knowledge, ours is the first report from a
prospective observational studies corrected for the regression dilution
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Beever G, Lip GY, O’Brien E. ABC of hypertension: the pathophys-
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5. Conclusion
This study revealed that D-dimer level was higher among
hypertensives than control groups and it was also increasing
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Author contributions
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Data curation: Yanli Long, Yi Li.
Funding acquisition: Litao Zhang.
Investigation: Liang Tao.
Methodology: Hongyan Xiao.
Project administration: Ying Li.
Resources: Yi Li.
Software: Litao Zhang.
Supervision: Liang Tao.
Validation: Hongyan Xiao.

Visualization: Chunyou Zhou.
Writing—original draft: Yanli Long.
Writing—review and editing: Chunyou Zhou.

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