

Venous thromboembolism – a manifestation of the metabolic syndrome

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ABSTRACT

Background and Objectives

The metabolic syndrome, defined by abdominal obesity, elevation of blood pressure, fasting glucose and triglycerides and low levels of high-density lipoprotein cholesterol is associated with atherosclerotic disease. It induces a pro-inflammatory and pro-thrombotic state. Despite its high prevalence, data on the association with venous thromboembolism (VTE) are scarce. The aim of our study was to elucidate the association of the metabolic syndrome with the risk of VTE.

Design and Methods

We conducted a case-control study to investigate the presence of the metabolic syndrome defined according to guidelines of the National Cholesterol Education Program, in high-risk patients with objectively confirmed recurrent VTE, who had had at least one unprovoked event of deep venous thrombosis or pulmonary embolism. Age and sex-matched healthy individuals served as controls.

Results

A total of 116 patients and 129 controls were enrolled. The prevalence of the metabolic syndrome was statistically significantly higher in patients (40/116, 35%) than in controls (26/129, 20%, $p=0.012$). The unadjusted odds ratio (OR) of the metabolic syndrome for VTE was 2.1 (95% CI [1.2–3.7], $p=0.012$) and remained statistically significant after adjustment for established thrombosis risk factors, sex and age (OR=2.2, 95% CI [1.1–4.3], $p=0.020$). Individuals with the metabolic syndrome ($n=66$) had significantly higher levels of high-sensitivity C-reactive protein (median, [interquartile range]: 0.312 mg/dL, [0.142–0.751] vs. 0.153 mg/dL, [0.073–0.330], $p<0.001$), fibrinogen (390 mg/dL, [342–432] vs. 343 mg/dL, [310–394], $p<0.001$) and factor VIII activity (182%, [157–216] vs. 159%, [133–199], $p=0.005$) compared to those without ($n=179$).

Interpretation and Conclusions

The metabolic syndrome may contribute to the development of VTE and is associated with a two-fold increased risk of VTE.

Key words: metabolic syndrome, deep venous thrombosis, pulmonary embolism, thrombophilia, venous thromboembolism

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Venous thromboembolism (VTE) is a common disorder in developed countries, with an annual incidence of 1 – 2 events per 1000 people in the general population.¹ It constitutes a major health concern due to its high prevalence, morbidity and mortality. VTE is a multifactorial disease with both inherited and acquired thrombophilic risk factors playing important roles.² However, there is still a large number of patients with deep venous thrombosis (DVT) and pulmonary embolism (PE) in whom no risk factor can be identified. There is accumulating evidence for an association between VTE and atherosclerosis.³⁻⁷ VTE and atherosclerosis may share common risk factors. For example, obesity in general and abdominal obesity in particular are also well accepted risk factors for VTE and were reported to be associated with impaired fibrinolytic activity, which may be a predisposing mechanism to arterial as well as to venous thrombosis.⁸⁻¹² Two recent studies again dissent to demonstrate a relationship between subclinical atherosclerosis and VTE.^{13,14}

The metabolic syndrome, which has received increased attention in the past few years, is a cluster of interrelated risk factors of metabolic origin for atherosclerotic disease and type 2 diabetes mellitus, comprising abdominal obesity, elevated blood pressure, high triglycerides, reduced levels of high-density lipoprotein cholesterol (HDL-C) and elevated fasting glucose plasma levels.^{15,16} Metabolic syndrome is diagnosed if three of these characteristics are present. In several studies the metabolic syndrome was also identified as an independent risk factor for stroke.¹⁷⁻¹⁹ The prevalence of the metabolic syndrome is rising and this syndrome is becoming a considerable burden on health economies in developed countries. For instance, more than 20% of the adult population in the United States have the metabolic syndrome.²⁰ In many individuals with the metabolic syndrome elevations of plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and clotting factors VII and VIII are found^{16,21-23} which might shift blood homeostasis to a hypercoagulable state and favor the development of VTE. Data from only one study on the association of the metabolic syndrome with VTE are currently available.²⁴ In that study, patients with a history of DVT had a higher prevalence of the metabolic syndrome than had control subjects.

However, the significance of the metabolic syndrome for the development of VTE remains to be further elucidated. We investigated the association of the metabolic syndrome, diagnosed on the basis of definition of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), with VTE in a high-risk population of thrombosis patients with a history of objectively confirmed recurrent VTE and at least one unprovoked event of DVT or PE.

Design and Methods

Study Population

We conducted a case-control study. The study protocol was approved by the Ethics Committee of the Medical University of Vienna prior to enrollment of the patients. One hundred and forty-six consecutive outpatients with a history of objectively confirmed recurrent VTE, who had at least one unprovoked event of DVT or PE and were referred to our department for an assessment of thrombosis risk factors between January 2003 and December 2004, were potentially eligible for our study. These patients were invited by letter to participate. Finally, 116 (79%) of them accepted our invitation. Enrollment took place between January 2005 and November 2005. The study was explained to each participant in a personal interview. The patient's medical history was collected by standardized questionnaire and from medical records on the day of study inclusion. VTE was denoted as unprovoked if there was no known triggering condition, such as surgery, trauma causing immobilization, pregnancy, delivery or malignancy. VTE that occurred during oral contraception use or hormone replacement therapy was considered to be unprovoked, but these treatments had to be completed at least 3 months before study inclusion to avoid any influence on serum lipid levels. The diagnosis of VTE had to be verified by at least one objective method in all cases and events. The methods used were duplex ultrasonography or venography for DVT and angiography, spiral computed tomography or combined ventilation/perfusion-scan for PE. Consecutive thrombotic events were only denoted as recurrent VTE if the time period between the first and second event exceeded three months. Study participants had to be at least 18 years old and had to consent to participation in the study. The time-interval between the most recent event of VTE and blood collection had to be at least 3 months. Exclusion criteria were current pregnancy or delivery within the past 3 months, chronic renal or liver disease, underlying disorders such as malignancy, overt infection and autoimmune diseases and surgery or trauma within 3 months prior to blood sampling.

Healthy individuals (n=129) without a medical history of VTE or arterial thrombosis from the same geographic region and ethnic background as the patients served as controls and were matched for age and sex. The control group was interviewed regarding a history of arterial or venous thrombosis or pulmonary embolism. A previous thrombotic event was ruled out when the medical history was, without doubt, negative. Individuals in this reference group had to be unrelated to patients. They were either spouses or acquaintances of patients, hospital staff, or friends or relatives of the hospital staff. Control individuals were not related to each other. All participat-

ing patients and controls gave written informed consent prior to inclusion in the study.

Measurements

Venous blood samples were obtained by sterile antecubital venepuncture after overnight fasting for at least 10 hours between 08:00 a.m. and 10:00 a.m. on the day of study inclusion. Routine blood tests, lipid analyses, plasma glucose assay and coagulation screening tests were performed immediately. Serum total cholesterol (mg/dL) and triglyceride (mg/dL) levels were evaluated by an automated enzyme analyzer (Olympus AU 5000, Japan) and low-density lipoprotein cholesterol (LDL-C) (mg/dL) and HDL-C (mg/dL) by turbidimetric assays (Olympus AU 5000, Japan). Fasting plasma glucose (mg/dL) was measured by glucose hexokinase assays (Olympus AU 5000, Japan). Height (m) and weight (kg) were recorded and the body mass index (BMI) was calculated (kg/m^2). Normal weight was defined as a BMI between 20.00 and 24.99 kg/m^2 , overweight as a BMI between 25.00 and 29.99 kg/m^2 and obesity as a BMI above 30.00 kg/m^2 .²⁵ Blood pressure (mmHg) and waist and hip circumferences (cm) were measured by trained staff, using the same instruments for all participants. The waist circumference was measured with a measuring tape as described by Ashwell *et al.*²⁶ The waist-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. Blood pressure was measured in the right upper arm after 15 minutes' rest using a mercury sphygmomanometer with a cuff of a standard size or an appropriately sized cuff for a larger upper arm circumference. The presence of the metabolic syndrome in patients and controls was documented according to the NCEP ATP III criteria reported in the latest American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) statement based on clinical measures including waist circumference, and levels of triglycerides, HDL-C, blood pressure and fasting glucose.¹⁶ The presence of three or more characteristics constituted the diagnosis of metabolic syndrome, the characteristics being: (i) elevated waist circumference (central obesity): ≥ 102 cm in men, ≥ 88 cm in women; (ii) elevated triglycerides: ≥ 150 mg/dL or drug treatment for elevated triglycerides; (iii) reduced HDL-C: < 40 mg/dL in men, < 50 mg/dL in women or drug treatment to reduce HDL-C; (iv) elevated blood pressure: ≥ 130 mmHg systolic blood pressure or ≥ 85 mmHg diastolic blood pressure or drug treatment for hypertension; (v) elevated fasting glucose: ≥ 100 mg/dL or drug treatment for elevated glucose).

Established risk factors for VTE (protein C-, protein S- or antithrombin-deficiency, lupus anticoagulant, elevated homocystein levels, factor V Leiden and prothrombin G20210A variation) were routinely determined in every patient and control after enrollment, as previously described.²⁷ Factor VIII activity was measured on a

Sysmex CA 7000 analyzer using factor VIII-deficient plasma (Hyland Baxter Immuno, Vienna, Austria) and Dade® Actin® -FS (Dade Behring, Marburg, Germany). The cut-off point for elevated factor VIII activity was set at 229%, which represents the 95th percentile of factor VIII activity in our controls (n=129). High-sensitivity C-reactive protein (hs-CRP) was measured by fully automated particle enhanced immunonephelometry (N High Sensitivity CRP, Dade Behring®) on a Behring Nephelometer II (BN Systems®).²⁸

Statistical Methods

Binary logistic regression analysis was applied to calculate univariable and multivariable odds ratios (OR) of the metabolic syndrome and of each component of the metabolic syndrome for VTE (dependent variables) and corresponding 95% confidence intervals (CI). The multivariable model included the following independent variables: age, sex, factor V Leiden and prothrombin G20210A variation (categorized at two levels: heterozygous or homozygous mutation carrier or carrier of normal variant, respectively) and factor VIII (categorized at two levels: activity above or below 229%). Categorical parameters were compared among groups by the χ^2 test, continuous variables with a normal distribution by the t-test and continuous variables with a skewed distribution by the Mann-Whitney test, respectively. A two-tailed *p*-value of less than 0.05 was considered to indicate statistical significance. All tests were performed with the statistical package SPSS 12 for Windows®.

Results

We enrolled 116 patients with a history of objectively confirmed recurrent VTE and 129 healthy individuals. Table 1 displays the basic characteristics of patients and controls and shows data on established risk factors for VTE. As expected, factor V Leiden, prothrombin G20210A variation, elevated factor VIII activity and hyperhomocysteinemia were more prevalent in patients than in controls. In 34 (29%) patients, no risk factor for thrombosis was detected. Fibrinogen ($p < 0.001$) and hs-CRP levels ($p = 0.006$) were statistically significantly higher in patients than in controls. Seven patients (6%) also had a history of arterial thrombosis: two had had thrombosis of a peripheral artery, one had had a stroke and four had had a myocardial infarction. Triggering events and sites of the thrombotic events are listed in Table 2. Eighty-eight (75.9%) of the first episodes and 106 (91.4%) of the second episodes of VTE were unprovoked. In most patients the site of thrombosis was the deep veins of the leg. The mean age (\pm SD) of patients at the time of their first and second episodes was 42 (± 14) and 49 (± 13) years, respectively. Twenty-nine patients with recurrent VTE (25%) had had more than two events. The median time interval

Table 1. Basic characteristics of patients and controls and established risk factors for venous thromboembolism.

	Patients n=116	Controls n=129	p
Age at study entry, years, mean \pm SD	56 \pm 12	53 \pm 11	n.s.
Gender, female, n (%)	53 (45.7)	66 (51.2)	n.s.
Positive smoking status, n (%)	30 (25.9)	28 (21.7)	n.s.
Fibrinogen levels, mg/dL, mean \pm SD	393 \pm 82	346 \pm 59	<0.001
hs-CRP levels, mg/dL, median (IQR)	0.229 (0.100-0.540)	0.150 (0.074-0.352)	0.006
Risk factors for VTE, n (%)			
FV: R506Q mutation			
heterozygous	41 (35.3)	13 (10.1)	<0.001
homozygous	3 (2.6)	0 (0)	
FII : G20210A mutation			
heterozygous	14 (12.07)	4 (3.1)	0.008
homozygous	2 (1.72)	0 (0)	
Protein C deficiency	1 (0.9)	0 (0)	n.s.
Protein S deficiency	4 (3.4)	1 (0.8)	n.s.
Antithrombin deficiency	1 (0.9)	0 (0)	n.s.
Lupus anticoagulant	5 (4.3)	0 (0)	0.023
Hyperhomocysteinemia*	20 (17.2)	4 (3.1)	<0.001
Elevated factor VIII level	25 (21.6)	6 (4.7)	<0.001
Number of combined risk factors			<0.001
Two risk factors combined	27 (23.3)	2 (1.6)	–
Three risk factors combined	2 (1.72)	0 (0)	–

*defined as values above 12.4 μ mol/L for women and above 15 μ mol/L for men.

between the most recent event of VTE and study entry was 2.55 years [interquartile range (IQR): 1.58 – 5.36]. At the time of study inclusion, 67% of patients (78 of 116) were being treated with oral anticoagulants (OAC). The proportion of active smokers was not significantly different between patients (26%) and controls (22%, $p=0.4$).

Patients with VTE had statistically significantly higher BMI, WHR and triglyceride levels. Total serum cholesterol, LDL-C, fasting glucose, and systolic and diastolic blood pressure were not statistically different between patients and controls. HDL-C was statistically significantly lower in patients than in controls. All values are summarized in Table 3. At the time of study inclusion eight patients and four controls were receiving therapy with statins, 27 patients and 19 controls were receiving antihypertensive therapy and in five patients and two controls antidiabetic therapy was ongoing.

The metabolic syndrome was diagnosed in 40 (35%) of 116 patients and in 26 (20%) of 129 controls ($p=0.012$). The prevalence of each component of the metabolic syndrome in patients and controls and the association of these components with the risk of VTE are listed in Table 4. The unadjusted OR of the metabolic syndrome was statistically significantly associated with VTE (OR=2.1, 95% CI [1.2-3.7], $p=0.012$). After adjustment for established risk factors, factor V Leiden, prothrombin G20210A variation and elevated factor

Table 2. Triggering events of VTE and site of thrombotic episode of VTE.

	First episode of VTE n (%)	Second episode of VTE n (%)
Unprovoked	80 (68.97)	105 (90.52)
oral contraceptive hormone replacement therapy	7 (6.03)	1 (0.86)
Trauma	10 (8.62)	1 (0.86)
Surgery	9 (7.76)	6 (5.17)
Pregnancy	3 (2.59)	0 (0)
Puerperium	2 (1.72)	0 (0)
Others [§]	4 (3.45)	3 (2.59)
Isolated DVT*	88 (75.86)	87 (75)
Combined PE and DVT*	18 (15.52)	16 (13.79)
Isolated PE	9 (7.76)	12 (10.34)
Other location of VTE	1 (0.86) [‡]	1 (0.86) [‡]
Age at time of episode, years, mean \pm SD	42 \pm 14	49 \pm 13

[§]Other triggering conditions such as long distance flight and immobilization; *All deep vein thrombosis (DVT) of the leg; [‡]Thrombosis of the mesenteric veins; [†]Brachial vein thrombosis.

VIII activity, sex and age the association remained statistically significant (OR=2.2, 95% CI [1.1–4.3], $p=0.020$). When the metabolic syndrome was adjusted alone for BMI the association of the metabolic syndrome with VTE was of borderline statistical significance (OR=1.9 (95% CI [1.0–3.7], $p=0.056$).

The metabolic syndrome was present in 27% of the whole study population (n=245). Individuals with the metabolic syndrome (n=66) had statistically significantly higher hs-CRP (0.312 mg/dL [0.142–0.751] vs. 0.153 mg/dL [0.073–0.330], $p<0.001$), fibrinogen (390 mg/dL [342–432] vs. 343 mg/dL [310–394], $p<0.001$) and factor VIII activity (182 % [157–216] vs. 159 % [133–199], $p=0.005$) compared to those without the metabolic syndrome (n=179). Furthermore, individuals with the metabolic syndrome were significantly older in comparison to those without (60 years [53–64] vs. 52 years [44–61], $p<0.001$). The presence of the metabolic syndrome was statistically significantly associated with the BMI ($p<0.001$): 3% of 31 study participants with a normal weight (BMI <25 kg/m²), 29% of 59 study participants who were overweight (BMI 25 kg/m²–29.99 kg/m²) and 73% of 26 obese study participants (BMI >30 kg/m²) had the metabolic syndrome.

Discussion

Our current study shows an association of the metabolic syndrome with the risk of VTE. The prevalence of the metabolic syndrome was significantly higher in patients with objectively confirmed recurrent VTE than in control subjects without a history of venous or arte-

Table 3. Values of body mass index, waist-hip ratio, waist and hip circumference, fasting glucose, systolic and diastolic blood pressure, total serum cholesterol, LDL-C, HDL-C and triglycerides in patients and controls.

	Patients n = 116	Controls n = 129	p
Body mass index (BMI) kg/m ² , median (IQR)	27.41 (24.78-29.70)	25.80 (23.69-29.37)	0.040
Waist-hip ratio (WHR) mean (±SD)	0.92 (±0.08)	0.89 (±0.09)	0.006
Waist circumference cm, mean (±SD)	99.3 (±14)	93.7 (±13)	0.001
Hip circumference cm, mean (±SD)	108.1 (±9.7)	105.5 (±9.6)	0.370
Fasting glucose mg/dL, mean (±SD)	100 (±19)	97 (±16)	0.143
Systolic blood pressure mmHg, mean (±SD)	132 (±19)	128 (±16)	0.178
Diastolic blood pressure mmHg, mean (±SD)	83 (±11)	82 (±10)	0.573
Total serum cholesterol mg/dL, median (IQR)	233 (204-262)	230 (197-255)	0.186
LDL-cholesterol mg/dL, median (IQR)	146 (120-172)	141 (118-157)	0.110
HDL-cholesterol mg/dL, median (IQR)	56 (48-64)	60 (51-71)	0.034
Triglycerides mg/dL, median (IQR)	136 (100-188)	112 (84-158)	0.005

rial thrombosis. The presence of the metabolic syndrome was independently associated with a two-fold higher risk of VTE, in multivariate analysis adjusted for established risk factors, factor V Leiden, the prothrombin G20210A variation and elevated factor VIII activity, sex and age. This association was virtually not attenuated even after adjustment for BMI, bearing in mind that an elevated waist circumference, as one component of the metabolic syndrome, also characterizes obesity. In separate evaluations, three of the five individual components of the metabolic syndrome were associated with VTE. Nevertheless, the metabolic syndrome was

demonstrated to have the strongest association with VTE, which would argue in favor of the hypothesis that it is not the presence of a single component, but rather the constellation of multiple components of the metabolic syndrome that is crucial.²⁹

Up to now the metabolic syndrome as a risk factor for VTE has been evaluated in only one Italian case-control study by Ageno *et al.*²⁴ In that study patients, in whom DVT was verified by compression ultrasonography, were compared to control subjects with suspected DVT, in whom the diagnosis of DVT was excluded. The results were very similar to those of our study concerning the magnitude of the risk (OR=1.9, 95% CI [1.0–3.6] in the Italian study vs. OR=2.2, 95% CI [1.1–4.3] in our study). Interestingly, the prevalence of the metabolic syndrome among patients and controls in the Italian study was higher than the prevalence among patients and controls in our study. This might be due to the fact that the Italian patients and controls were older than those in our study. Another difference between the Italian study and ours is the time period of study inclusion. In the study by Ageno *et al.* the time period between the thrombotic event and the study inclusion with data collection is not reported exactly; however, most probably patients and controls were investigated for the presence of the metabolic syndrome in close proximity to the case-defining event. We performed our specimen collection at least 3 months after acute event of VTE to avoid any influences of the acute event on diagnostic criteria of the metabolic syndrome. Additionally, the groups of Italian patients and controls were not matched for sex, as they were in our study and Italian patients had a first VTE, whereas we studied patients with recurrent VTE.

Our results indicate that age is clearly associated with the occurrence of the metabolic syndrome. As it is strongly believed that VTE is a multifactorial disease with involvement of genetic, acquired and environmental factors, the higher prevalence of the metabolic syndrome at a higher age could be one of the explanations for the increasing incidence of VTE with increasing age.

Table 4. Frequency of each component of the metabolic syndrome (any three of the five criteria constitute a diagnosis of metabolic syndrome) and the association with VTE.

	Number of individuals (%)		Univariable OR (95 % CI)	p	Multivariable OR (95 % CI)	p
	Patients (n=116)	Controls (n=129)				
Metabolic syndrome	40 (35%)	26 (20%)	2.1 (1.2-3.7)	0.012	2.2 (1.1-4.3)	0.020
Elevated waist circumference	60 (51%)	53 (41%)	1.5 (0.9-2.5)	0.095	1.7 (0.9-3.1)	0.084
Elevated triglycerides	54 (44%)	38 (30%)	2.1 (1.2-3.5)	0.006	1.9 (1.1-3.5)	0.030
Reduced HDL-C	24 (21%)	13 (10%)	2.3 (1.1-4.8)	0.021	1.9 (0.8-4.3)	0.145
Elevated blood pressure	62 (53%)	59 (46%)	1.4 (0.8-2.3)	0.228	1.2 (0.7-2.2)	0.559
Elevated fasting glucose	37 (32%)	26 (20%)	1.9 (1.0-3.3)	0.036	2.0 (1.0-3.8)	0.041

¹The metabolic syndrome and each component of the metabolic syndrome were adjusted for factor V Leiden, prothrombin G20210A variation, elevated factor VIII activity, sex and age.

Similarly, it can be hypothesized that the higher prevalence of the metabolic syndrome in overweight and obese individuals could be closely linked to the well-known higher risk of VTE in overweight and obese patients. The important underlying pathophysiological mechanism could be mediated through hypercoagulability due to increased levels of fibrinogen and factor VIII and decreased fibrinolytic potential.^{16, 21-23, 30, 31}

Our study has several limitations. First of all, it is a retrospective case-control study and we included patients with a history of recurrent VTE. Data should be verified in prospective studies on patients with primary and recurrent VTE. However, our results correspond very well with those from Ageno *et al.*, who similarly performed a case-control study but included patients with a first VTE. We tried to eliminate any influence of a recent thrombotic event.

The metabolic syndrome is a well-known risk factor for the development of atherosclerotic cardiovascular disease. Our data and those from the literature may strengthen the hypothesis of an association between atherosclerosis and venous thrombosis, which is the subject of animated discussion.^{3-7,13,14,32,33} Analyzing the components of the metabolic syndrome individually, abdominal obesity was demonstrated to be of predictive value for both coronary heart disease and VTE.^{9,34} Dyslipidemia has long been known to be a risk factor for atherothrombotic disorders.³⁵ An unfavorable lipid profile may also have an effect on the risk of VTE.³⁶⁻³⁹ Arterial hypertension and diabetes have also been found to be associated with VTE.^{40,41}

We were able to measure hs-CRP, fibrinogen and factor VIII activity in our study and these parameters were

significantly elevated in the subgroup of individuals with the metabolic syndrome, which is concordant with previously reported data.^{16, 21-23, 30, 31} People with the metabolic syndrome frequently have a pro-inflammatory state, as shown by increased acute-phase reactants (e.g., CRP, fibrinogen),^{30,31} and also a prothrombotic state due to elevated levels of fibrinogen, PAI-1, and clotting factors.^{16, 21-23} Both pro-inflammatory and prothrombotic states are thought to be critical for the development of VTE. In conclusion, our study suggests that the metabolic syndrome, beside its well-recognized impact on atherosclerotic cardiovascular and cerebrovascular disease and type 2 diabetes mellitus, is also a considerable risk factor for VTE and might contribute to the multifactorial pathogenesis of VTE. Consequentially, early identification, treatment and prevention of the metabolic syndrome including lifestyle changes and management for controlling the components of the syndrome, are major challenges. The aim is to prevent not only type 2 diabetes, cardiovascular disease and cerebrovascular disease, but also VTE.

Authors' Contributions

CA: designed and performed the research, analyzed data and wrote the manuscript; TT: performed the research and wrote the manuscript; RV: performed the research, analyzed data and wrote the manuscript; RS: performed the research and wrote the manuscript; WD: designed the research, analyzed data and wrote the manuscript; TV: provided vital analytical tools, analyzed data and wrote the manuscript; IP: designed and performed the research, analyzed data and wrote the manuscript

All authors approved the final version to be published.

Conflict of Interest

The authors reported no potential conflicts of interest.

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