

Can whole blood viscosity predict the development of acute mesenteric arterial thrombosis?

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ABSTRACT

BACKGROUND: Acute mesenteric ischemia is a serious condition with high mortality rate, resulting internal organ damage and intestinal necrosis due to sudden occlusion in the arteries feeding the abdominal solid organs and intestines. The most common causes of acute mesenteric artery ischemia are embolic processes and thrombosis that develops on the basis of primary mesenteric artery atherosclerosis. Whole blood viscosity (WBV) was defined by De Simon and could be calculated with a formula that consists of total plasma protein and hematocrit (HCT). In our study, we aimed to investigate the predictive value of WBV for acute mesenteric ischemia caused by primary mesenteric artery occlusion.

METHODS: Between January 2015 and February 2021, a total of 55 patients with a retrospective diagnosis of acute mesenteric ischemia (AMI) and 50 healthy volunteers as a control group were included in the study. WBV was calculated with the De Simon formula using the HCT and plasma protein levels from the blood tests of healthy volunteers and patients at the time of admission with acute abdomen.

RESULTS: No significant differences between the two groups in terms of baseline demographic characteristics except the prevalence of age (72.1 ± 12.4 vs. 65.7 ± 6.4 ; $p < 0.001$) and hypertension (40% vs. 23% $p = 0.002$). AMI patients had significantly higher WBV values both at low shear rate (LSR) (46.3 ± 21.7 vs. 33.4 ± 13.1 , $p < 0.001$) and high shear rate [HSR] (16.5 ± 11 vs. 15.8 ± 0.7 , $p < 0.001$). The univariate analysis identified several variables for predicting AMI including age (odds ratio [OR]: 1.066 confidence interval [CI]: 1.023–1.111, $p = 0.003$), hypertension (OR: 3.612 CI: 1.564–8.343, $p = 0.003$), WBV at HSR (OR: 2.074 CI: 1.193–3.278, $p = 0.002$), and WBV at LSR (OR: 2.156 CI: 1.331–3.492, $p = 0.002$). However, after multivariate analysis, only hypertension (OR: 3.537 CI: 1.298–9.639, $p = 0.014$) and age (OR: 1.085 CI: 1.026–1.147, $p = 0.004$) showed significance. In receiver operating characteristic analysis, a cut-off value of 43.5 WBV for LSR had a 72% sensitivity and a 70% specificity for prediction of mesenteric ischemia patients (area under curve [AUC]: 0.743, $p < 0.001$) and a cut-off value of 16.29 WBV for HSR had a 78% sensitivity and 76% specificity for prediction of mesenteric ischemia patients (AUC: 0.773, $p < 0.001$).

CONCLUSION: In our study, we determined that the WBV value obtained with the De Simon formula is a valuable parameter in predicting the development of acute mesenteric artery ischemia caused by primary mesenteric artery occlusion.

Keywords: Acute mesenteric ischemia; de simon formula; whole blood viscosity.

INTRODUCTION

Mesenteric ischemia is circulatory system disease that is mostly seen in the elderly with generalized abdominal pain. Acute mesenteric ischemia (AMI) occurs when mesenteric circulation, which supplies the demands of visceral organs,

abruptly deteriorates. If urgent therapy is not provided, prognosis is poor with a mortality rate of 60%–80%.^[1] Acute mesenteric ischemia is classified into four: mesenteric arterial thrombosis due to embolism (50% of all cases), mesenteric artery thrombosis (15%–25%), mesenteric venous thrombo-

Cite this article as: Gul S, Kucuk GO. Can whole blood viscosity predict the development of acute mesenteric arterial thrombosis? *Ulus Travma Acil Cerrahi Derg* 2023;29:685-690.

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Ulus Travma Acil Cerrahi Derg 2023;29(6):685-690 DOI: 10.14744/tjtes.2023.92837 Submitted: 30.06.2022 Revised: 09.09.2022 Accepted: 16.04.2023
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sis (5%–15%), and nonocclusive mesenteric ischemia (5%–15%).^[2,3]

In thromboembolic mesenteric ischemia, embolic process is thought to be associated with left atrium if patients have atrial fibrillation, left ventricle in heart failure setting, prosthetic valves, endocarditis, rheumatic valve disease, and aortosclerosis.^[4]

Besides, smoking, hypertension, hyperlipidemia, diabetes, chronic renal failure, antiphospholipid syndrome, hypercoagulability, and low cardiac output contribute to both thromboembolic mesenteric ischemia and primary mesenteric artery occlusion.^[3,4] On the other hand, situations that impair perfusion such as cardiogenic shock, diuretic drug usage, and emergent cardiac surgery are mostly associated with nonocclusive mesenteric ischemia.^[4,5]

The association of hemorheological factors with atherosclerotic process was demonstrated by clinical studies.^[6] The Virchow triad, which plays a role in etiology of many vasoocclusive diseases, consists of three parameters hypercoagulability, endothelial dysfunction, and stasis. Thrombus formation based on hypercoagulability and increased whole blood viscosity (WBV) that provide a basis for endothelial shear stress are associated with many cardiovascular diseases.^[7]

WBV was defined by De Simon and could be calculated with a formula that consists of total plasma protein and hematocrit (HCT) endothelial shear stress has two components: impact at peak point of systolic blood pressure (high shear rate [HSR]) and impact at diastolic blood pressure (low shear rate [LSR]).^[8]

In our study, we aimed to investigate the predictive value of WBV for acute mesenteric ischemia.

In our study, we aimed to investigate the predictive value of WBV for acute mesenteric ischemia due to primary mesenteric artery occlusion.

MATERIALS AND METHODS

Study Population

Seventy consecutive patients who admitted to emergency room between January 2015 and February 2020 with abdominal pain and diagnosed with mesenteric ischemia were enrolled for retrospective analysis. The virtual hospital data archive, demographic data, medical history, cardiovascular risk factors, and laboratory data at the time of the patient was diagnosed with acute mesenteric ischemia were scanned. Six patients with venous mesenteric ischemia, seven patients who were on anticoagulant therapy, seven patients using anticoagulant therapy for atrial fibrillation, and one patient who had chronic heart failure were excluded from study. Fifty individuals who were healthy and well-matched for sex and age included to the control group. The study protocol was approved by the Institutional Ethics Committee.

Exclusion Criteria

Exclusion criteria were atrial fibrillation, use of anticoagulants, left ventricular hypertrophy (septal thickness > 13 mm), chronic infectious diseases, malignancy, autoimmune diseases, peripheral artery diseases, chronic renal failure, severe valvular heart disease, and prosthetic valve diseases. The reason we excluded these patients was these conditions are inflammatory processes that may affect WBV.

Clinical Evaluation

Mesenteric ischemia was diagnosed by a detailed physical examination, laboratory tests, and abdominal ultrasonography. Ultrasonography is valuable for proximal arterial flow assessment; however, the evaluation of distal arterial segment flow is sometimes complicated. Furthermore, in obese patients, in situations with excessive intra-abdominal gas and densely calcified arteries, ultrasonography is not convenient. All patients underwent computerized tomography angiography to confirm diagnosis. Patients were followed up at general surgery ward. All patients left ventricle ejection, and heart valves were evaluated with echocardiography (Vivid 9, GE VingMedUltrasound, Horten, Norway). Plasma total protein (TP) levels and HCT values at the beginning of hospitalization with the diagnosis of acute mesenteric ischemia were obtained from the hospital virtual laboratory data archive and recorded in the data form. The erythrocyte count, hemoglobin, HCT, and white blood cell count were measured using the automated hematology analyzer XE-1200 (Sysmex, Kobe, Japan). Biochemical measurements were performed with a molecular analyzer (Roche Diagnostics, Mannheim, Germany).

Whole Blood Viscosity Measurement

WBV is calculated with De Simone formula.^[8]

WBV at both HSR (HSR=208/s-1) and LSR (LSR=0.5/ s-1).

For HSR: WBV (208 s-1)=(0.12×HCT)+0.17×(TP-2.07), for LSR: WBV (0.5 s-1)=(1.89×HCT)+3.76×(TP-78.42).

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Comparison of quantitative data between groups (with normal distribution) was done by utilizing Student's t-test. In case of nonparametric distribution, data were analyzed with the Mann-Whitney U test. Categorical data were compared by Chi-square test. The univariate analysis was performed on different factors associated with AMI. Variables in which the unadjusted p-value had reached statistical significance (p<0.05) were included in the full multivariate models. Two different logistic regression models were composed separately for LRS and HSR: WBV at HSR in Model 1 and WBV at LSR in Model 2. Independent risk factors affecting outcome were calculated by multivariate logistic regression analysis and comparative results were presented. The best cut-off value for both LSR and HSR regarding clinical outcome was exam-

Table 1. Baseline characteristics and laboratory findings of the study population

Parameters	Study groups		p
	AMI patients (n=55)	Control patients (n=50)	
Age (years), mean±SD	72.1±12.4		
65.7±6.4	<0.001		
Men, n (%)	30 (54.5)	21 (42)	0.19
HTN, n (%)	40 (75.5)	23 (46)	0.002
DM, n (%)	23 (41.8)	15 (30)	0.21
Atrialfibrillation, n (%)	21 (38.9)	19 (38.8)	0.99
Smoking, n (%)	17 (31)	23 (46)	0.11
LDL-C (mg/dL)	98.85±22.9	106.1±27.7	0.16
Triglyceride (mg/dL)	150.7±90.9	141.7±18.1	0.49
Hemoglobin (g/dL)	13.8±1.7	13.6±0.6	0.65
Hematocrit (%)	42±5.7	41±2.2	0.27
Total protein (g/L)	69.9±5.3	67.9±4.6	0.06
Platelets (103 µl)	252.1±107.1	249.4±64.1	0.87
Creatinine (mg/dL)	1.48±1.21	1.52±1.22	0.85
LVEF (%)	52.17±10.7	53.2±7.9	0.58

Data are given as mean±SD, median (IQR) or n (%). IQR: Interquartile range, SD: Standard deviation, AMI: Acute mesenteric ischemia, DM: Diabetes mellitus, HTN: Hypertension, LDL-C: Low-density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction, HPL: Hyperlipidemia, BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol, AAO: Acute arterial occlusion.

ined by receiver operating characteristic analysis. Odds ratios (ORs) and 95% confidence intervals were calculated; sensitivity and specificity values for outcome classification were created. Statistical significance was demonstrated if $p < 0.05$.

RESULTS

Baseline characteristics and laboratory findings of both groups is presented in Table 1. No significant difference between the two groups in terms of basic demographic characteristics was detected, except for prevalence of age (72.1±12.4 vs. 65.7±6.4; $p < 0.001$) and hypertension (40% vs. 23% $p = 0.002$). AMI patients had significantly higher WBV values both at LSR

(46.3±21.7 vs. 33.4±13.1, $p < 0.001$) and HSR (16.5±1.1 vs. 15.8±0.7, $p < 0.001$) (Table 2 and Fig. 1).

Several variables for predicting AMI including age, hypertension, WBV at HSR, and WBV at LSR ($p < 0.05$) were identified by univariate analysis (Table 3). We designed two models derived from a multivariate analysis on the predictors of WBV parameters for each shear rate, which are illustrated in Table 4. In Model 1, which described WBV at LSR, following parameters: age, hypertension, and WBV at HSR were found to be independent predictors of AMI. The second model (WBV at HSR) demonstrated that age, hypertension, and WBV at LSR were also independent predictors for AMI. In both models,

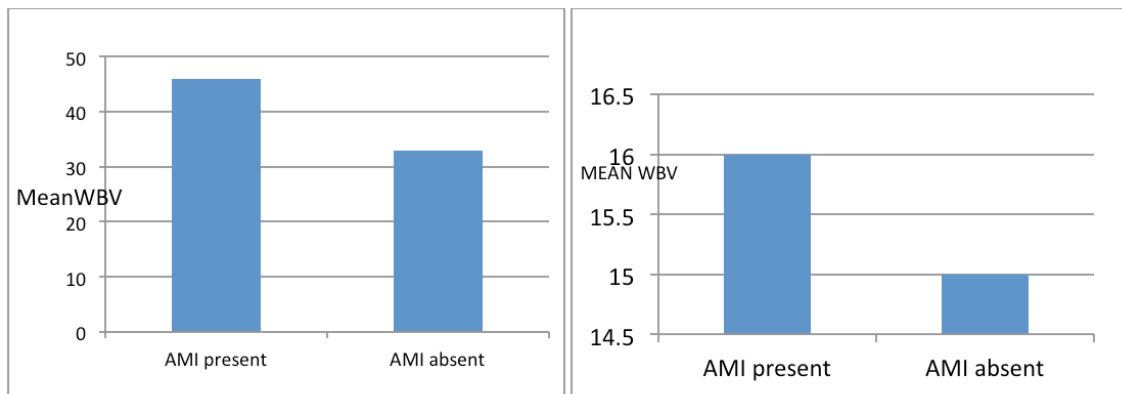


Figure 1. (a) WBV levels at LSR in both groups; (b) WBV levels at HSR in both groups. LSR: Low shear rate; WBV: Whole blood viscosity; HSR: High shear rate.

Table 2. Comparison of whole blood viscosity parameters of the study group

Variables	AMI absent	AMI present	p
WBV at LSR (0.5/s-1)	33.4±13.1	46.3±21.7	0.001
WBV at HSR (208/s-1)	15.8±0.7	16.5±1.1	0.001

WBV at HSR: Whole blood viscosity at high shear rate; WBV at LSR: Whole blood viscosity at low shear rate; AMI: Acute mesenteric ischemia.

WBV was an independent predictor of AMI ($p<0.05$) (Table 4).

A cut-off value of 43.5 WBV for LSR had a 72% sensitivity and a 70% specificity for prediction of mesenteric ischemia patients (area under curve [AUC]: 0.743, $p<0.001$) and a cut-off value of 16.29 WBV for HSR had a 78% sensitivity and 76% specificity for prediction of mesenteric ischemia patients (AUC: 0.773, $p<0.001$) (Fig. 2).

DISCUSSION

To our knowledge, this is the first study that evaluates WBV in AMI patients. Our results show that WBV which is cal-

culated with De Simon formula for both LSR and HSR is an independent predictor for acute mesenteric ischemia due to primary mesenteric artery occlusion.

Acute mesenteric artery ischemia is mostly due to a plaque rupture located at superior mesenteric artery, inferior mesenteric artery or truncus coeliacus, or a cardiac embolism to aforementioned arteries that impair organ perfusion. Clinical projections are mainly generalized abdominal pain, nausea, vomiting, and if not treated; death by intestinal necrosis is nearly inevitable. Most important risk factors are smoking, hyperlipidemia, diabetes, hypertension, chronic renal failure, hypercoagulability, low cardiac output, and antiphospholipid syndrome.^[9] Embolic process is the most frequent reason

Table 3. Effects of variables on clinical outcomes for acute mesenteric ischemia in univariate logistic regression analysis

Variables	OR	95% CI	p
Age	1.066	1.023–1.111	0.003
HT	3.612	1.564–8.343	0.003
WBV at LSR (0.5/s-1)	2.074	1.193–3.278	0.002
WBV at HSR (208/s-1)	2.156	1.331–3.492	0.002

WBV at HSR: Whole blood viscosity at high shear rate, WBV at LSR: Whole blood viscosity at low shear rate. OR: Odds ratio, CI: Confidence interval, HT: ???

Table 4. Effects of variables on clinical outcomes for acute mesenteric ischemia in multivariate logistic regression

Variables	OR	95% CI	p
MODEL 1			
HTN	3.537	1.298–9.639	0.014
Age	1.085	1.026–1.147	0.004
WBV at LSR	2.053	1.149–3.418	0.004
MODEL 2			
Hypertension	3.200	1.178–8.696	0.023
Age	1.080	1.024–1.139	0.005
WBV at HSR (208/s-1)	2.139	1.244–3.676	0.006

WBV at HSR: Whole blood viscosity at high shear rate; WBV at LSR: Whole blood viscosity at low shear rate; HTN: Hypertension; OR: Odds ratio; CI: Confidence interval.

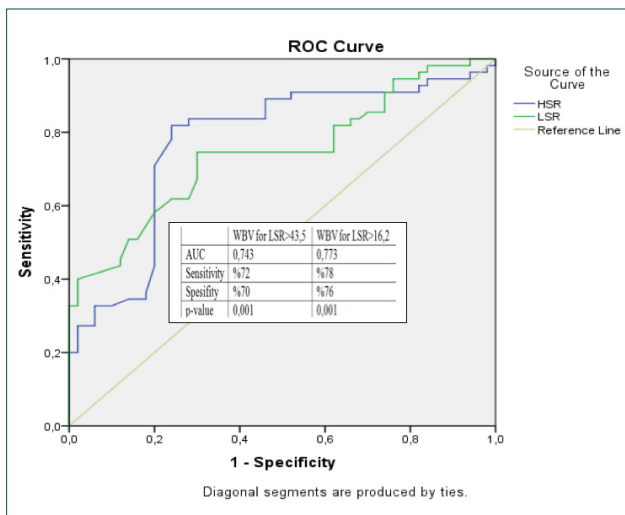


Figure 2. Receiver operating characteristic curve analysis showing the predictive cut-off value of WBV at a high shear rate (blue line) and low shear rate (green line) for AMI patients. AUC: Area under the curve; HSR: High shear rate; LSR: Low shear rate; WBV: Whole blood viscosity; AMI: Acute mesenteric ischemia.

(50%) for mesenteric artery occlusion. Embolism mostly origins from left atria if patient had atrial fibrillation or left ventricle in heart failure setting. Prosthetic heart valves and infective endocarditis are other underlying conditions for cardiac embolisms. In 15%–25% of acute mesenteric ischemia cases, atherosclerosis is the underlying mechanism of arterial occlusion. Vulnerable plaque rupture then thrombosis leads to arterial occlusion and perfusion impairment. As a result, atherosclerosis and thrombosis play a major role in the pathogenesis of acute mesenteric artery occlusion.^[2-4]

WBV is determined by two factors: plasma viscosity which is related with plasma protein level and HCT which is the percent of blood cells in whole blood. One can measure WBV with complex devices^[10] or can calculate simply by a formula defined by De Simone.^[8] This formula was validated in studies investigating various conditions, coronary slow flow phenomenon, heart failure, myocardial infarction, mitral annular calcification.^[11]

The determinant factor for endothelial shear stress is the WBV.^[12-14] Increase in WBV leads to decrease in blood fluidity and this brings out decrease in endothelial shear stress and stasis eventually. As luminal stasis increases endothelial dysfunction and atherosclerotic process advances. As a result, the Virchow triad is completed. Laminary blood flow becomes turbulent and this leads to more deformation in endothelial structure and functions. In the end, small amounts of thrombotic material progressively accumulate in distal vascular bed.^[15]

In a study that compares patients who suffered from acute myocardial infarction with healthy individuals, calculated WBV was found to be significantly higher than controls.^[16] In another study, WBV was found to be related with susceptibility for deep vein thrombosis.^[17] Along with the development

of endothelial dysfunction, lipoproteins start to accumulate in subendothelial region and at the end of this inflammatory process atherom plaques occur. There are substantial data demonstrating the correlation between increased inflammatory gene expression and LSR.^[18] Supported by the data from aforementioned studies about WBV, it is suggested that various cardiovascular conditions are related with WBV by atherosclerotic and inflammatory pathways.^[7] In our study, we determined that complete WBV is an independent parameter with high predictive value in predicting acute mesenteric artery ischemia due to mesenteric artery occlusion.

Many studies demonstrated the relationship between HTN and cardiovascular diseases. HTN is the most common risk factor.^[19] Our data which is consistent with the results of other studies showed that the frequency of HTN determined high rate in AMI patients compared to control group. It is known that AMI occurs more frequently in the elderly. Arterial blood flow deteriorates with advancing age due to the progression of atherosclerosis, endothelial dysfunction, disruption of laminar blood flow, and plaque rupture complication. In our study, having higher average age in AMI group than control group supported that age is an independent risk indicator for acute mesenteric ischemia. In this study, we found that WBV increased in acute mesenteric artery occlusion due to inflammatory mechanisms in the development process of atherosclerosis.

Limitations

Main limitations of this study are low number of patient population, single center data, and retrospective method. Furthermore, other hemorheological factors that may affect blood viscosity such as platelet and erythrocyte agreeability and rigidity were not evaluated. Another minor limitation is the method for calculating WBV. Gold standard for this calculation is the direct measurement with viscometer; nonetheless, many other clinical studies used De Simone formula like we did and found the results consistent with device measurements.

Conclusion

Our results showed that WBV was significantly elevated in both HSR and LSR conditions in patients with AMI, resulting from primary mesenteric artery occlusion. This study is the first in field and may be accepted as an inspiration for prospective and larger clinical trials on this subject.

Ethics Committee Approval: This study was approved by the Samsun Training and Research Hospital Clinical Research Ethics Committee (Date: 27.05.2020, Decision No: 33646832-799).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.G., G.O.K.; Design: S.G.; Supervision: S.G., G.O.K.; Resource: S.G., G.O.K.; Materials: G.O.K., S.G.; Data: S.G., G.O.K.; Analysis: S.G.; Literature search: S.G., G.O.K.; Writing: S.G., G.O.K.; Critical

revision: S.G., G.O.K.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study has received no financial support.

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ORIJİNAL ÇALIŞMA - ÖZ

Tam kan viskozitesi akut mezenterik arter trombozu gelişimini öngörebilir mi?

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AMAÇ: Tam kan viskozitesi (WBV), kardiyovasküler olayların güçlü bir tahminicisidir. Akut mezenterik iskemide, abdominal organları ve bağırsakları besleyen arterlerde ani tıkanmaya bağlı olarak iç organ hasarı ve bağırsak nekrozu ile sonuçlanan, mortalite oranı yüksek, ciddi bir durumdur. Bununla birlikte, kan viskozitesi ile akut mezenterik iskemide (AMI) arasındaki ilişki şimdiki kadar yeterince çalışılmamıştır. Çalışmamızda, mezenterik arterin primer aterosklerotik tıkanıklığından kaynaklanan akut mezenterik iskemide için WBV'nin prediktif değerini araştırmayı amaçladık.

GEREÇ VE YÖNTEM: Bu çalışma, Ocak 2015-Şubat 2021 tarihleri arasında (AMI) tanısı almış toplam 55 hasta ve kontrol grubu olarak 50 sağlıklı erişkin üzerinde yapıldı. Tam kan viskozitesi, karın ağrısı ile acile başvuran ve tetkikler sonucunda akut mezenterik iskemide teşhisi konulan hastaların kan testlerinden hematokrit ve plazma protein seviyeleri kullanılarak De Simone formülü ile hesaplandı.

BULGULAR: Yaş (72.1±12.4 ve 65.7±6.4; p<0.001) ve hipertansiyon (%40 ve %23 p=0.002) dışında başlangıç demografik özellikleri açısından iki grup arasında anlamlı fark saptanmadı. Tam kan viskozitesinin hem düşük kesme hızında (LSR) ((46.3±21.7 vs. 33.4±13.1, p<0.001) hem de yüksek kesme hızında (HSR) (16.5±1.1 vs. 15.8±0.7, p<0.001) AMI hastalarında anlamlı olarak daha yüksek olduğu hesaplandı.

Tek değişkenli lojistik regresyon analizinde, AMI'yi öngörmeye yaş (OR: 1.066 CI: 1.023-1.111, p=0.003), hipertansiyon (OR: 3.612 CI: 1.564-8.343, p=0.003), HSR'de WBV (OR: 2.074 CI: 1.193-3.278, p=0.002) ve LSR'de WBV (OR: 2.156 CI: 1.331-3.492, p=0.002) değerlerinin anlamlı değişkenler olduğu tespit ettik. Ancak çok değişkenli analizden sonra sadece hipertansiyon (OR: 3.537 GA: 1.298-9.639, p=0.014) ve yaş (OR: 1.085 GA: 1.026-1.147, p=0.004) anlamlılık gösterdi. ROC analizinde, LSR için 43.5 kesim değeri, mezenterik iskemide hastalarında %72 duyarlılığa ve %70 özgüllüğe (eğri altındaki alan (EAA): 0.743, p<0.001) ve HSR için 16.29 kesim değerinin %78 duyarlılığa ve %76 özgüllüğe sahip olduğunu tespit ettik (EAA: 0.773, p<0.001).

TARTIŞMA: Çalışmamızda De Simone formülü ile elde edilen WBV değerinin primer mezenterik arter tıkanıklığından kaynaklanan akut mezenterik arter iskemisinde gelişimini öngörmeye değerli bir parametre olduğunu belirledik.

Anahtar sözcükler: Akut mezenterik iskemide; de simon formülü; tam kan viskozitesi.

Ulus Travma Acil Cerrahi Derg 2023;29(6):685-690 doi: 10.14744/tjtes.2023.92837