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A Novel Predictor of Vegetation Size in Infective Endocarditis: MAPH Score

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ABSTRACT

The aim of this study is to evaluate the predictive value of the MAPH score in patients with, a novel score that includes blood viscosity biomarkers such as hematocrit, mean platelet volume (MPV), age, and total protein, on the extent of vegetation in infective endocarditis. This study was retrospective. Fifty-four patients older than 18 years who were diagnosed with infective endocarditis (IE) between June 2017 and June 2023 were included. The study included patients from three different tertiary healthcare centers. Hematocrit, C-reactive Protein (CRP), MPV, total protein, serum albumin, kidney and liver function tests were analyzed on the first day of hospitalization. The Youden Index was used to determine the cut points for predicting age and MPV, hematocrit and total protein values for vegetation size. The MAPH score has been calculated as a total of 0 or 1 point with the cutoff in each ratio, and values above the cut-off were considered 1 point. Thirty-eight patients were found to have large vegetations (>10 mm). The mean age of the patients was 54.78 ± 17.32 years. The other clinical characteristics and demographic data were similar to each other. total protein level, MPV, and MAPH score were significantly higher in the vegetation size >10 mm group than in the vegetation size ≤ 10 mm group when analyzing the clinical laboratory characteristics of the study.
The results of our study were that the MAPH score can be used as an estimate of the extent of vegetation cover.

Keywords: Infective endocarditis, MAPH score, Vegetation size

Introduction

Infective endocarditis (IE) is called infection of the heart endothelium. The incidence and mortality of infectious endocarditis remain high (1). In the general population, the annual incidence is 3-10/100,000. 30-day mortality can be as high as 30% (2,3). Healthcare-related IE now accounts for 25-30% of the contemporary cohort. This is because of the increasing use of intracardiac instruments and intravenous catheters (4). *Staphylococcus aureus*, accounting for ~26.6% of all cases, is now the most frequently cause of IE in most studies. It is followed by viridans group streptococci, enterococci and other streptococci (3). Although its sensitivity is variable, modified Duke criteria are used in the diagnosis of IE (5). A sensitivity of 80% is achieved in cases of implantable electronic device infections or prosthetic valve endocarditis (PVE) (6,7).

High-risk patients are selected based on the presence of IE complications (cerebral hemorrhage, septic shock, heart failure or renal failure), findings obtained by echocardiography (pseudoaneurysm significant valve damaged or abscessed), specific patient characteristics (PVE, age or comorbidities), and the responsible organism (S. *aureus*, gram-negative bacilli, and non-*Haemophilus* spp, *Cardiobacterium, Actinobacillus spp, Kingella spp, E.corroden*s, fungi). The size and mobility of the vegetation have been associated with complications of systemic embolization. European guidelines accept 10 mm as the threshold for needing early intervention with appropriate antibiotic treatment for proven systemic embolism, although clinically 4 mm vegetation is associated with silent neurological embolism (8,9). Vegetation size and neurological complications are also linearly related. Neurological complications are observed with vegetations >30 mm in up to 60% of patients (10). The MAPH score is a novel scoring system that

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assesses some biomarkers of blood viscosity (hematocrit, MPV, and total protein) combined with age. Blood viscosity may play an essential role in the pathophysiological process of vegetation formation. In addition, it has been reported that this score may be useful in early diagnosis in a study of whether it can be used as a predictor of thrombus burden in patients with ST-segment elevation myocardial infarction (STEMI) (11). This study investigated whether the MAPH score, which combines blood viscosity biomarkers can predict vegetation size in infective endocarditis.

Materials and Methods

This retrospective study was conducted between June 2017 and June 2023. It included 54 patients over 18 years of age who had been diagnosed with IE. The study included patients from three different tertiary healthcare centers. Patients were categorised into two groups according to vegetation size. Vegetation size was ≤10mm in 16 patients and >10mm in 38 patients. Patients with a known history of hematology, inflammation, or malignancy, severe liver or kidney impairment, poor echocardiography image quality, or missing records for the specified parameters were excluded from the study. Patients' medical records and routine laboratory parameters were analyzed for demographic and medical characteristics.

The modified Duke criteria defined IE as two major findings or one major and three minor or five minor findings. High blood pressure (HT) was defined as blood pressure ≥140/90 mm Hg or taking antihypertensive medication. The definition of diabetes mellitus was the use of antidiabetic medication or the presence of fasting serum glucose ≥126 mg/dL and HbA1c ≥6.5%. Haematocrit, serum albumin, total protein, MPV, lipid profiles, CRP, renal and liver parameters were analyzed on the first day of hospitalization. The Youden index was used to calculate predictive cut points of age, haematocrit , MPV, and total protein for vegetation size. The MAPH score is new and easily accessible. It is calculated by adding haematocrit and total protein, MPV values, and age. Each ratio was calculated as 0 or 1 point with a cut-off point and values higher than the cut-off point were accepted as 1 point.

The local ethics committee approved the study protocol on 14/07/2023 with decision number 456. Patient informed consent was waived. The study was retrospective, observational, part of a routine hospital laboratory procedure, and patient information was kept confidential. The Declaration of Helsinki was followed in this study.

Statistical Analysis: IBM SPSS Statistics 25.0 was used. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to examine the normality of numerical variables. The t-test or Mann-Whitney U test was used to compare two groups regarding numerical variables, depending on their suitability. The The Pearson chi-square test and Fisher's exact test were used to analyse the relationships between the categorical variables.Age, MPV, hematocrit, total protein; cutoff, specificity, sensitivity, area under the curve (AUC), and 95% CIs were evaluated using ROC analysis. The cut-off value was determined using the Youden index. Descriptive data are expressed as median (min-max) values for variables that are not normally distributed, and as mean ± standard deviation (SD) values for continuous variables that are normally distributed. The correlation between vegetation size and MAPH score was analysed using the Pearson correlation test. The r and p values that were obtained were recorded. In addition, the correlation result was presented using a scatterplot, and the R2 linear value was reported. Values $p<0.05$ were regarded as statistically significant.

Results

In this study, 54 patients older than 18 years of age diagnosed with infective endocarditis were included. A comparison of the basic and demographic characteristics of the patients is shown in Table 1. The mean age was 54.78±17.32 years and 31.5% of the patients were female. The vegetation size was ≤ 10 mm in 43.8% and > 10 mm in 26.3% of female patients (p=0.208). Other clinical characteristics and demographics were not significantly different. Clinical laboratory findings of the study: total protein values, MPV, and MAPH score were significantly higher in vegetation size >10 mm group compared to vegetation size ≤ 10 mm group (respectively p= 0.014, p= 0.032, p= 0.005) (Table-2).

In the ROC analysis, MPV was 74% sensitivity, 69% specificity (AUC: 0.758, 95%CI: 0.614-0.903, p=0.003), age 75% sensitivity, 37% specificity (AUC: 0.483, 95%CI: 0.308-0.657, p =0.842), total protein 63% sensitivity, 69% specificity (AUC: 0.710, 95%CI: 0.565-0.854, p=0.016), hematocrit 66% sensitivity, 56% specificity (AUC: 0.648, 95%CI: 0.491-0.805, p=0.088) was associated with vegetation size (Figure-1). Additionally, MAPH was associated with vegetation size with

Table 1. Comparison of Basic and Demographic Characteristics of Patients

Parameters	Vegetation Size ≤ 10 mm (n=16)	Vegetation Size > 10 mm (n=38)	Total (n=54)	p-value
Age, year	54.4±19.1	54.9±16.7	54.7±17.3	0.926
Female, n (%)	7 (43.8)	10 (26.3)	17 (31.5)	0.208
Hypertension, n (%)	8 (50.0)	11 (28.9)	19 (35.2)	0.139
Diabetes Mellitus, n (%)	6 (37.5)	12 (31.6)	18 (33.3)	0.673
CKD, n (%)	7 (43.8)	14 (36.8)	21 (38.9)	0.634
Chronic Hemodialysis Patients, n (%)	1 (6.3)	3 (7.9)	4 (7.4)	0.660*
Intravenous Drug Use, n (%)	0	2 (5.3)	2 (3.7)	0.491*
Central Venous Catheter, n (%)	0	1 (2.6)	1 (1.9)	0.704*
CAD, n (%)	2 (12.5)	6 (15.8)	8 (14.8)	0.756
Heart failure, n (%)	2 (12.5)	9 (23.7)	11 (20.4)	0.351
CHD, n (%)	1 (6.3)	4 (10.5)	5 (9.3)	0.621
Pacemaker, n (%)	0	1 (2.6)	1 (1.9)	0.704*
Heart Prosthetic Valve, n (%)	1 (6.3)	3 (7.9)	4 (7.4)	0.660*
Rheumatic Heart Valve, n (%)	1 (6.3)	5 (13.2)	6 (11.1)	0.461
Bicuspid Aortic Valve, n (%)	0	1 (2.6)	1 (1.9)	0.704*
Atrial Fibrillation, n (%)	1 (6.3)	3 (7.9)	4 (7.4)	0.660*
COPD, n (%)	0	4 (10.5)	4 (7.4)	0.306*

CKD: Chronic Kidney Disease; CAD: Coronary Artery Disease; CHD: Congenital Heart Disease; COPD: Chronic Obstructive Pulmonary Disease
*Fischer Exact Test

66% sensitivity and 81% specificity (AUC: 0.734, 95%CI: 0.586-0.881, p=0.007) (Figure 2). Pearson correlation analysis was also used to examine the relationship between vegetation size and MAPH score. There was a moderate correlation (r=0.305; p=0.025) between vegetation size and MAPH score. In addition, 93% of the variation in vegetation size was associated with MAPH score (R2 linear: 0.093) according to linear regression analysis and scatterplot (Figure 3).

Discussion

The main conclusions of our study are that the levels of total protein, MPV, and MAPH were substantially higher in the group with vegetation > 10 mm than in the group with vegetation ≤ 10 mm. As a result, the MAPH score in IE was an important indicator in estimating vegetation size, which is a predictor of mortality. The association between vegetation size and MAPH score in IE was investigated for the first time in this study. Understanding the risk of embolization in IE, i.e. estimating the size of the vegetation, helps the physician to appropriately classify patients as at risk and facilitates treatment decisions in patients with a vegetation size >10 mm. In a meta-analysis of 21 studies evaluating the correlation between vegetation size and embolic risk in IE, embolic and mortality rates were significantly higher in patients with vegetation size >10 mm (9). The predictive validity of the MAPH score was also found to be high in patients with a high level of thrombus load in a study of patients diagnosed with non-STEMI (12). Another study concluded that the MAPH score could be a biomarker for estimating thrombus load in patients with STEMI (11). In addition, the MAPH score was found to be associated with slow coronary flow (13). MPV measures platelet size and is an important factor in platelet activity (14). In several heart diseases, raised MPV is associated with poor outcomes.

Table 2: Comparison of Patients Physical Examination, Imaging and Laboratory Results

Parameters	Vegetation Size ≤ 10 mm (n=16)	Vegetation Size > 10 mm (n=38)	Total (n=54)	p-value
Septic Cerebral Embolism, n (%)	1 (6.3)	4 (10.5)	5 (9.3)	0.621
Septic Peripheral Embolism, n (%)	2 (12.5)	5 (13.2)	7 (13.0)	0.948
Splenic Abscess, n (%)	0	1 (2.6)	1 (1.9)	0.704*
Splinter Hemorrhage, n(%)	1 (6.3)	3 (7.9)	4 (7.4)	0.660*
Janeway lesion, n (%)	0	1 (2.6)	1 (1.9)	0.704*
Osler's nodule, n (%)	0	1 (2.6)	1 (1.9)	0.704*
Glomerulonephritis, n(%)	0	2 (5.3)	2 (3.7)	0.491*
Aortic Valve Vegetation, n (%)	4 (25.0)	12 (31.6)	16 (29.6)	0.629
Mitral Valve Vegetation, n(%)	11 (68.8)	23 (60.5)	34 (63.0)	0.568
Tricuspid Valve Vegetation, n (%)	3 (18.8)	8 (21.1)	11 (20.4)	0.848
Prosthetic Valve Vegetation, n (%)	0	2 (5.3)	2 (3.7)	0.491*
WBC, x10³/μL	10.5±6.1	12.9±5.3	12.2±5.6	0.150
Hemoglobin, g/dL	9.6±1.7	10.7±2.1	10.4±2.1	0.059
Hematocrit, %	29.8±4.9	33.2±6.2	32.2±6.0	0.061
Platelet, x10³/μL	208±96	170±103	181±102	0.225
MPV, fL	8.5±1.2	9.4±1.0	9.1±1.1	0.014
Glucose, mg/dL	123±93	109±29	113±55	0.564
Creatinine, mg/dL, (IQR)	1.05 (1.0)	1.10 (0.9)	1.10 (0.9)	0.641
Total Protein, g/dL	6.2±0.7	6.7±0.8	6.5±0.8	0.032
Albumin, g/dL	2.98±0.55	2.90±0.67	2.92±0.64	0.685
D-dimer, μg/L	709.6±197.6	746.9±302.8	736.4±275.9	0.672
CRP, mg/L, (IQR)	12.0 (10.5)	14.4 (16.0)	13.4 (14.5)	0.236
Sedimentation, mm/h, (IQR)	50.0 (65.0)	74.0 (49.0)	67.0 (47.0)	0.577
MAPH Score	1.88±0.95	2.68±0.90	2.44±0.98	0.005

WBC: White Blood Cell; MPV: Mean Platelet Volume; CRP: C-reactive Protein
*Fischer Exact Test

Han et al. showed that coronary heart disease and stroke were more frequent in MPV > 8FL (15). Another study on the prediction of MI and stroke reported that MPV should not be considered insignificant (16). The study found that high MPV was considerably higher in the vegetation size >10 mm group than in the vegetation size ≤10 mm group. All thromboembolic events are at high risk with increasing age, with 65 years being the cut-off age (17). Studies have shown that age is an important determinant of morbidity and mortality in people with acute myocardial infarction (18,19). The mean age in our study was 54.78 ± 17.32 years. The major serum elements are albumin, fibrinogen, and globulins, which regulate plasma viscosit. Globulins carry elements such as lipid, protein, copper and iron within their structure, while fibrinogen plays a role in blood clotting. Serum proteins other than albumin were found to be higher in patients with acute stroke according to Briley et al. (20). A study conducted in 2019 associated beta-2 microglobulin concentrations with the Gensini score in patients with acute coronary syndrome (21). The relationship between

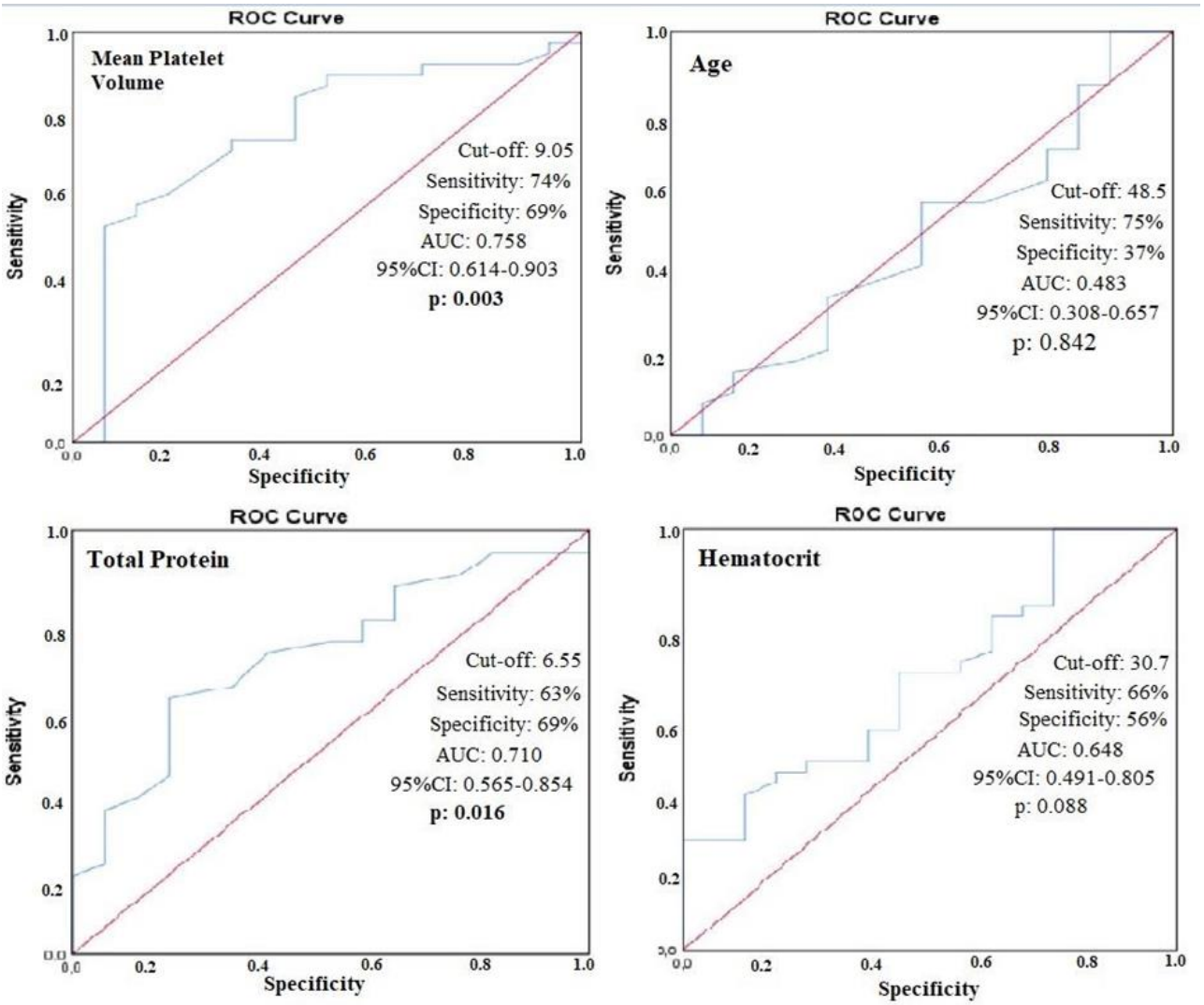

Fig. 1. ROC analysis showing the relationship of mean platelet volume, age, total Protein, and hematocrit with vegetation size group

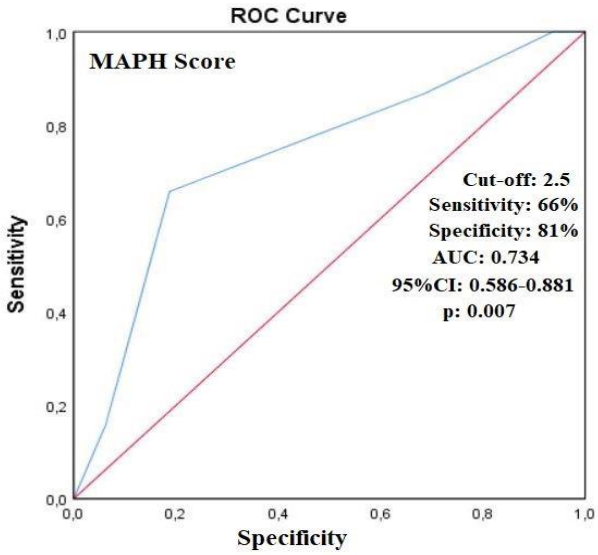

Fig. 2. ROC analysis showing the relationship of MAPH score with vegetation size group

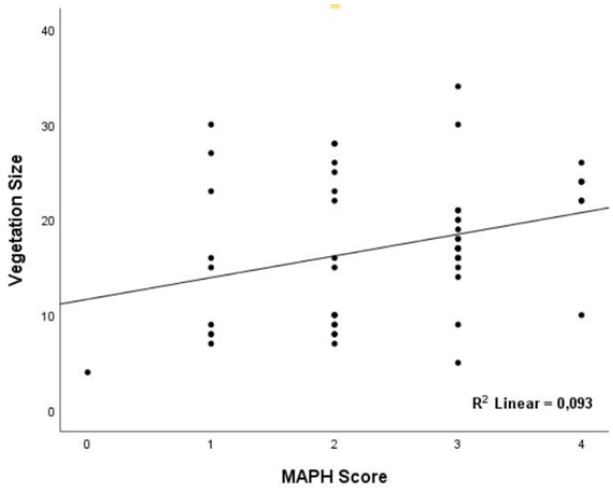

Fig. 3. Scatter-Dot plot showing correlation between vegetation size group and MAPH score

total protein levels and thrombus burden classification was investigated in another study. The conclusion of this study was that there was a positive correlation (11). In our study, total protein levels were one of the most important biomarkers for the prediction of thrombus size. Studies have shown that the risk of thrombosis increases with a high hematocrit (22,23). This increased risk is directly associated with males. However, the same result was observed in women with a low hematocrit as well as in women with a very high hematocrit. Similarly, in another study of women aged <65 years, higher haematocrit levels were a better determinant of cardiovascular mortality (24). All these data support the hypothesis of our study.

There are some limitations to our study. The study was a retrospective study and the number of people involved was small. The MAPH score, a new biomarker, requires cut-off points for each ratio. Multicentre and prospective studies with larger numbers of participants are needed to disseminate the MAPH score.

In conclusion, we found that the MAPH score predicts vegetation size. The data from our study will be a guide for future studies and a contribution to the literature.

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Conflict of Interest: The authors have declared that they have no competing interests.

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