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The role of mean platelet volume (MPV) level as an independent predictor for varicocele in late adolescent



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ABSTRACT

Background: Recent studies have reported significant associations between varicocele and platelet volume indices (PVIs). PVIs are inexpensive and widely used indicators consisting of mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR) and are related to platelet volume and function. The possibility of PVIs as a predictor for varicocele is yet to be exposed. This study aimed to assess the role of PVIs as a predictor for varicocele in the late adolescent.

Methods: This retrospective case-control study involved 89 varicocele subjects (group I) and 89 healthy controls (group II) of similar age, stature, and body mass index. The data were consecutively taken from medical records at Bhayangkara Denpasar Hospital between January 2017 and May 2019. The diagnosis of varicocele was based on the findings from both physical examination and color doppler ultrasound (CDU). PVIs indicators

were analyzed among the two groups. Statistical analysis was performed using receiver operating characteristic (ROC) curve to determine optimum cut-offs, bivariate chi-square test, and multivariate analysis using binary logistic regression, with $p < 0.05$ considered statistically significant.

Results: ROC curve analysis showed optimum cut-offs of 8.05, 12.05, and 15.1 for MPV, PDW and P-LCR respectively (Youden index: 0.494, 0.326, 0.292; $p < 0.001$, $p < 0.001$, $p = 0.001$ respectively). Chi-square test showed significant associations between the PVIs indicators and varicocele ($p < 0.001$). Binary logistic regression analysis revealed that MPV level of ≥ 8.05 is an independent predictor for late adolescent varicocele (OR=6.001; 95%CI 2.547-14.139; $p < 0.001$).

Conclusion: MPV can be used as an independent predictor for assessing varicocele in the late adolescent.

Keywords: Mean Platelet Volume, Independent Predictor, Varicocele, Late Adolescent

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INTRODUCTION

Varicocele is defined as an abnormal dilatation and tortuosity of the vein in the pampiniform plexus of the spermatic cord.¹ It is considered to be the most common surgically manageable vascular cause of infertility.¹ Varicocele is diagnosed by scrotal physical examination and is based on the Dubin system and adjusted to the findings on scrotal palpation.^{2,3} The incidence of varicocele in the general population is 6-23%.² On the study of 7035 military recruits (aged > 18 years old) from six European countries, varicocele prevalence was recorded at around 15.7%.⁴

Varicocele is a progressive disease that begins to develop at puberty in early adolescence.^{5,6} Adolescent varicoceles are generally asymptomatic and are usually accidentally diagnosed on the medical check-up. The incidence of varicocele in adolescents in the world is estimated at 15%.⁵ Kumanov et al. reported the prevalence of varicoceles in Bulgarian adolescents aged 10-19 years at 7.9%.⁷ Another study by Alsaikhan showed a majority of varicoceles of 21.9% in adolescents aged 11 - 19 years.⁶ Varicocele incidence increases

by 10% for every decade of life.⁶ The data suggested that testicular venous incompetence rises with age, most likely due to venous valve aging.⁶ If not treated adequately over a long period, varicocele in adolescence can cause testicular dysfunction and lead to infertility.⁵ A total of 19-41% of men experience primary infertility and 80% of men with secondary infertility.⁸

The role of platelets has been extensively studied in vascular diseases.⁸ The platelet volume measure reflects platelet activity and can be assessed with platelet volume indices (PVIs).¹ PVIs, which consist of platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR), are standard indicators in describing platelet function in the pathophysiology of vascular diseases.^{1,8} Increased MPV is related to vascular disease's presence and prognosis, including peripheral artery, cerebrovascular, and coronary artery diseases.⁹ Previous studies have reported significantly higher MPV levels on varicocele patients compared to healthy controls.^{1,2,10-12} A more recent study suggested that MPV could represent an inexpensive marker that could be used in assessing

low-grade inflammation in patients with varicocele in the pathophysiology of varicoceles.¹³ In addition, it was also stated that MPV might be a significant predictor in patients with varicocele, but further studies are required to expose this relationship.¹³ To date, there has not been any study which was done to investigate the possibility of PVIs as a significant predictor for varicocele, especially in the late adolescent. Thus, this study aims to assess the role of PVIs as a predictor for varicocele in late adolescents for the first time in the literature.

METHODS

A retrospective case-control study was conducted. The data were consecutively taken from medical records at Bhayangkara Denpasar Hospital between January 2017 and May 2019. The study was accepted by the local ethics committee. The inclusion criteria were male police recruitment participants aged 15-19 years diagnosed with varicocele during the medical check-up and have a complete medical record. The study excluded varicocele patients with a history of systemic diseases such as coronary heart disease, hypertension, hyperlipidemia, peripheral vascular disease, diabetes mellitus, splenectomy, thrombotic thrombocytopenic purpura (TTP), idiopathic thrombocytopenic purpura (ITP), myeloproliferative disorders, leukemia, Bernard-Soulier syndrome, thrombocytopenia (thrombocytopenia) (thrombocytopenia (less than $150 \times 10^3 / \mu\text{L}$) or thrombosis (more than $450 \times 10^3 / \mu\text{L}$); patients with a history of diseases of the scrotum other than varicoceles (testicular tumors, hydrocele, undescensus testis, inguinal hernia, and epididymo-orchitis); patients with a history of surgery in the inguinal and scrotal areas; and patients with a history of epinephrine injection in the past month. A total of 89 samples were eligible to be included in the case group ($n=89$). The control group was selected among consecutive age-stature-BMI-matched male healthy participants with an even number ($n=89$).

The diagnosis of varicocele was based on the findings from the scrotal physical examination. It was categorized based on the Dubin grading system: Grade I: varicose veins are palpable only during the Valsalva maneuver. Grade II: varicose veins may be palpable during rest but not visible. Grade III: visible varicose veins. If the findings were inconclusive, a color doppler ultrasound (CDU) was done to confirm the diagnosis. PVIs indicators (MPV, PDW, and PLC-R) were obtained from the routine complete blood count (CBC) results on the medical record, which was measured within 2 hours of sampling during the medical check-up.

General demographic and clinical characteristics (stature, BMI, clinical manifestation, varicocele type, and varicocele grade) were also obtained and described. Body mass index was categorized based on the BMI-for-age 2-20 years boys growth chart of the Centres for Disease Control and Prevention (CDC), i.e., Obese (≥ 95 th percentile), Overweight (85th-95th percentile), Healthy Weight (5th-85th percentile)) and Underweight (<5 th percentile). Stature categorization was based on the CDC stature-for-age 2-20 years boys growth percentile chart, i.e., Short stature (<5 th percentile), Normal stature ($5\text{th} \leq x < 95$ th percentile), and Tall stature (≥ 95 th percentile).

SPSS software (ver.1.8.0 for Windows; SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Predictive properties of the PVIs were evaluated by receiver operating characteristic (ROC) analysis. The Youden index method was used to determine the optimum cut-off value. Independent variables affecting the occurrence of varicocele were then estimated in a risk analysis model using a chi-square test on the univariable model and binary logistic regression on the multivariable model. All analyses were performed at 0.95 confidence level. A statistically significant difference was accepted as $p < 0.05$.

RESULTS

Demographic and clinical characteristics of both groups are described in [Table 1](#). Similar age median of 18 years, Normal stature, and Normal Weight BMI in both groups were observed. In the varicocele group, 85 (96%) patients were asymptomatic, and only four patients (4%) were experiencing testicular discomfort. Almost all varicoceles are left-sided unilaterally (97%), with 56 patients on grade III varicocele (63%) and 31 patients on grade II (35%).

The PVIs (MPV, PDW, and PLC-R) ability to predict the occurrence of varicocele in late adolescents was investigated by ROC analysis, shown in [Figure 1](#). The threshold values for those with the area under the curve of > 0.6 were calculated using the Youden index Method, and the threshold value that gives the highest Youden Index will be chosen as a cut-off value for each PVIs ([Table. 2](#)). The optimum cut-off value that MPV could predict for varicocele occurrence was 8.05 (sensitivity: 73 %, specificity: 76.4%, $p < 0.001$, Youden Index: 0.494). The area under the curve (AUC) for MPV in the ROC curve was 0.817 (95%CI 0.775-0.878). The cut-off value for PDW was 12.05 (sensitivity: 46.1%, specificity 86.5%, $p < 0.001$, Youden Index: 0.326). The AUC for PDW in the ROC curve was 0.688 (95%CI 0.610-0.765). The cut-off value for PLC-R

was 15.1 (sensitivity: 83.1%, specificity 46.1%, $p = 0.001$, Youden Index: 0.292). The AUC for PLC-R in the ROC curve was 0.641 (95%CI 0.560-0.723).

A risk analysis model of the PVI's (MPV, PDW, and PLC-R) in varicocele among late adolescents was

done using a chi-square test for the univariable and binary logistic regression analysis the multivariable model (Table. 3). As a result, it was detected that the probability of varicocele occurrence was 6.001 (95% CI: 2.547–14.139, $p < 0.001$) times higher in late adolescents with an MPV value of 8.05 and above compared to late adolescents with an MPV value below 8.05.

Table 1. General characteristic of varicocele and control group

Variable	Varicocele Group (n = 89)	Control Group (n = 89)	p-value
Age, median (min,max) (year)	18 (16-19)	18 (15-19)	0.676*
Stature, n (%)			
Tall	0 (0%)	0 (0%)	
Normal	89 (100%)	89 (100%)	
Short	0 (0%)	0 (0%)	
BMI, n (%)			0,732**
Obesity	0 (0%)	0 (0%)	
Over Weight	0 (0%)	0 (0%)	
Normal Weight	85 (96%)	84 (94%)	
Under Weight	4 (4%)	5 (6%)	
Clinical Manifestation			
Asymptomatic	85 (96%)	-	
Testicular Discomfort	4 (4%)	-	
Varicocele Type			
Unilateral S	86 (97%)	-	
Unilateral D	1 (1%)	-	
Bilateral	2 (2%)	-	
Varicocele Grade			
I	2 (2%)	-	
II	31 (35%)	-	
III	56 (63%)	-	

Note:*Mann Whitney U test **Pearson's chi-square test

Abbreviation: BMI, body mass index

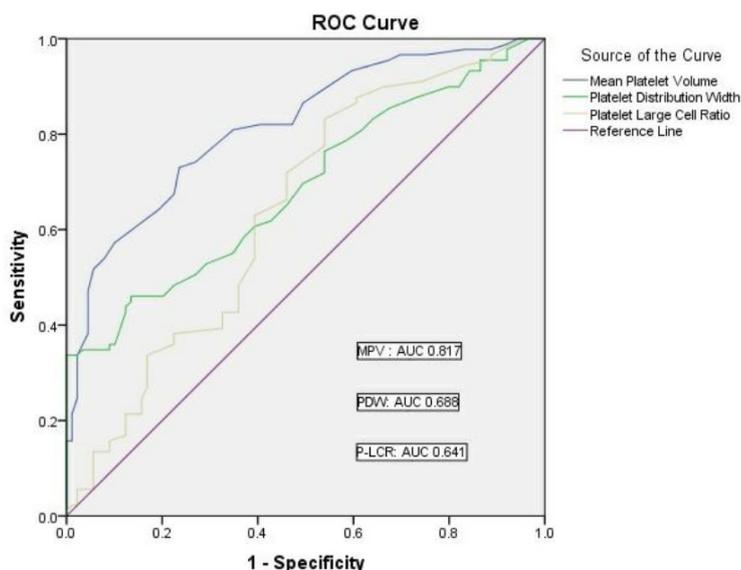


Figure 1. ROC analysis to predict the ability of PVI's on the occurrence of varicocele

DISCUSSION

The study of the relationship between platelet volume indices (PVI's) and varicocele was initially started by Bozkurt et al. (2012), who revealed a significantly higher MPV value in adults with varicocele compared to healthy adults in his preliminary study.¹⁰ Moreover, Coban et al. (2015) and Demirer et al. (2015) also reported similar results.^{2,11} In addition, Camoglio et al. (2015) reported the presence of a progressive age-related increase in MPV values on varicocele patients.¹⁴ Zafarghanti et al. (2014) found significantly higher MPV, PDW, and PLC-R on adults with varicocele compared to healthy adults.¹ Coban et al. (2015) reported that MPV increases in patients with varicocele and normalizes in 6 months post-surgically corrected varicocele patients.⁹ A systematic review and meta-analysis were conducted by Pyo et al. in 2016, which revealed significantly higher MPV in varicocele patients than in healthy subjects.¹² However, studies by Polat et al. (2016) and Okcelik et al. (2017) reported an insignificant relationship results between MPV level and varicocele.^{3,8} Polat stated that it might be due to a relatively small number of samples in his study.⁸ Okcelik's contrast result might be because of possible patient selection bias or other conditions which might affect MPV levels.³ A more recent study done by Demirer (2017) demonstrated a statistically higher MPV level in varicocele patients than in normal healthy controls.¹³ Furthermore, Demirer also determined the sensitivity and specificity levels for MPV in the prediction of varicocele (77% and 50%, respectively) and suggested that MPV could represent an inexpensive marker that could be used in assessing low-grade inflammation in patients with varicocele in the pathophysiology of varicoceles.¹³ In addition, Demirer also stated that MPV might be a significant predictor in patients with varicocele, but further studies are required to expose this relationship.¹³

In the present study, we investigated the role of PVI's (MPV, PDW, and PLC-R) as a predictor for varicocele in the late adolescent. Control by design on some of the possible confounding factors (age, stature, and BMI) was done by consecutively, including age-stature-BMI matched controls.^{7,14,15}

Table 2. The area under the curve (AUC) and optimum cut-off analysis

Parameter	AUC	95% CI	p	Cut-off	Sensitivity	Specificity	Youden's Index
MPV	0.817	0.775-0.878	< 0.001	8.05	0.730	0.764	0.494
PDW	0.688	0.610-0.765	< 0.001	12.05	0.461	0.865	0.326
P-LCR	0.641	0.560-0.723	0.001	15.1	0.831	0.461	0.292

Abbreviations: PVIs, platelet volume indices; MPV, mean platelet volume; PDW, platelet distribution width; P-LCR, platelet large cell ratio

Table 3. Risk analysis model of PVIs in varicocele among late adolescent

Parameter	Value	Univariable Model				Multivariable Model			
		Varicocele Group	Control Group	OR	95% CI	p	Adjusted OR	95% CI	p
		n (%)	n (%)						
MPV	≥ 8.05	65 (73%)	21 (23.5%)	8.77	4.455-17.262	< 0.001*	6.001	2.547-14.139	< 0.001*
	< 8.05	24 (27%)	68 (76.5%)						
PDW	≥ 12.05	41 (46%)	12 (13.5%)	5.48	2.622-11.458	< 0.001*	1.776	0.715-4.415	0.216
	< 12.05	48 (54%)	77 (86.5%)						
P-LCR	≥ 15.1	74 (83%)	48 (53.9%)	4.21	2.105-8.436	< 0.001*	1.227	0.513-2.938	0.645
	< 15.1	15 (17%)	41 (46.1%)						

Note:*Significant (p<0.05)

Abbreviations: PVIs, platelet volume indices; MPV, mean platelet volume; PDW, platelet distribution width; P-LCR, platelet large cell ratio

Similar age median of 18 years, Normal stature, and Normal Weight BMI on both groups were observed. The exclusion criteria of the samples also rule out other possible confounding factors. Our data showed that an MPV level of ≥ 8.05 is an independent predictor for late adolescent varicocele (OR=6.001; 95%CI 2.547-14.139; $p < 0.001$). To our knowledge, our study is the first one in the literature to assess the role of PVIs, particularly MPV, as a significant predictor for varicocele in late adolescence. Varicoceles in late adolescence are mostly asymptomatic. Therefore it is tough to detect without direct scrotal examination and could usually be done in military/police hospitals. Our institution is a public police hospital, where routine general check-ups are done on many police recruitment participants. Complete laboratory tests, including the complete blood count (CBC) are routinely done as standard requirements for the recruitment; therefore, we managed to obtain the necessary data for the present study. This study was inspired and done based on Demirer's statement in his previous study regarding MPV's possibility as a significant predictor in patients with varicocele. The present study demonstrated that Demirer's statement is possible, though other studies are needed to support it.

There is an essential limitation to this study. Other possible confounding factors such as smoking status couldn't be evaluated since it was not recorded on the medical record. In addition, the result of the present study can only be applicable to the late adolescent group. Therefore, there is a need for a prospectively planned study for evaluating

those other confounding factors, possibly with a higher number of samples and in other different age groups.

CONCLUSION

To our study, mean platelet volume (MPV) has a significant association with varicocele. Thus, MPV can be used as an independent predictor for assessing varicocele in the late adolescent.

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ETHICAL CLEARANCE

This study has obtained ethics approval.

CONFLICT OF INTEREST

We declare that there were no conflicts of interest in this study.

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AUTHOR CONTRIBUTION

All of the authors are equally contributed to the study.

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