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Diagnosis of Transmissible Venereal Tumors in Bitches - Platelet Indices Are a Remarkable Marker?

Serkan İrfan Köse[1], Ayşe Merve Köse[2], Ece Koldaş Ürer[2], Onur Bahan[3], Ahmet Gözer[2] & Pınar Ambarcıoğlu[4]

ABSTRACT

***Background*:** Hematological analyses are seen as more preferred laboratory analyses in canine transmissible venereal tumor studies. There is no information about the availability of platelets and their indices in routine practice in canine transmissible venereal tumor cases. Taking this as a starting point, this study analyzed the usefulness of platelet indices in dogs with transmissible venereal tumor in clinical laboratory diagnosis as well as examined the relationship between white blood cells, red blood cells, platelets (PLT), main platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), and the ratio of main platelet volume to platelets (MPV/PLT).

***Materials, Methods & Results*:** In the study, a total of 42 bitches of various breeds were used. Nineteen healthy bitches were used as a control group, and the others 23 with cTVT as a study group. Metastasis was not observed in any of the bitches involved in the study. History, clinical findings, and cytological examinations were evaluated for the diagnosis of cTVT. In animals with hemorrhagic discharge and neoplastic lesions, a vaginal cytological examination was performed. Typical TVT cells with large nuclei and intracytoplasmic vacuoles were observed in the vaginal cytological examinations, and the diagnosis of TVT was made. Healthy bitches (19) and those with TVT (23) were 39.16 5.37 months and 47.61 5.14 months old, respectively. From all animals, 2 mL blood samples were collected from V. cephalica to evaluate PIs in the complete blood count (CBC). Collected blood samples were analyzed using an automated hematology analyzer. As a result of the analysis, WBC, RBC, HGB, HCT, MCV, MCHC, RDW, PLT, MPV, PDW, PCT, and MPV/PLT data were obtained. Mild leukocytosis, an increase in PLT, and a decrease in MCV and MPV/PLT were determined in the study group compared to the control group. Cut-off values in CBC of bitches with TVT were determined as WBC: 13.35 (sensitivity: 78%; specificity: 90%); MCV: 67 (sensitivity: 57%; specificity: 95%); PLT: 315.50 (sensitivity: 65%; specificity: 74%); and MPV/PLT: 0.028 (sensitivity: 78%; specificity: 58%). In CBC analyses, a strong negative correlation between PLT and MPV/PLT was detected in both groups.

***Discussion*:** Canine transmissible venereal tumors are common in both stray and pet dogs. It is naturally transferred from animal to animal during mating by live tumor cells. This tumor can commonly affect the external genitalia and internal organs in some cases. It generally has the look of cauliflower, and its surface is ulcerated, inflammatory, hemorrhagic, and infectious. More preferred laboratory analyses are complete blood count and blood chemistry analysis in cTVT for to evaluate the success of treatments. Platelet indices have been investigated in many diseases such as endotoxemia, chronic enteropathy, mammary tumor, parvoviral enteritis, septic peritonitis, lymphoma, pyometra, visceral leishmaniasis, and babesiosis in dogs. There is no information available for either diagnostic or prognostic use of the PIs in canine TVT cases. Ultimately, in light of the presented study's results, platelet indices, especially PLT and the MPV/PLT ratio, seem to be notable laboratory markers in terms of easy accessibility and low-cost assessment techniques in canine transmissible venereal tumor cases. New data, however, should be established by a thorough follow-up study using a larger sample size and addressing its usefulness as a diagnostic or prognostic marker in canine transmissible venereal tumors.

Keywords: platelet indices, complete blood count, transmissible venereal tumor, female dog.

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[1]Department of Internal Medicine, [2]Department of Obstetrics and Gynecology & [4]Department of Biostatistics, Faculty of Veterinary Medicine, Hatay Mustafa Kemal University, Hatay, Türkiye. [3]Department of Obstetrics and Gynecology, Faculty of Veterinary Medicine, Yozgat Bozok University, Sorgun-Yozgat, Türkiye. CORRESPONDENCE: S.İ. Köse [serkanirfankose@mku.edu.tr & srknirfn@gmail.com]. Department of Internal Medicine, Faculty of Veterinary Medicine, Hatay Mustafa Kemal University. 31060 Hatay, Turkey.

INTRODUCTION

Canine transmissible venereal tumor (cTVT) is a type of reticuloendothelial tumor in dogs [13,35]. And, cTVT is the world's only known contagious tumor [43]. Tumor is more common in young, sexually active canines [1], and is naturally transferred during mating [2]. Tumor can commonly affect external genitalia, and also can be spread to the other organs (such as nasal or oral cavities, skin, etc.) via sniffing or licking [4,35,43]. Hemorrhagic discharge, neoplastic lesions, deformity of the external genitalia, foul odor are common clinical signs [13].

Modern hematology analyzers allow for the automated counting of blood cells via complete blood count (CBC) [34]. Different cell types may be easily examined using CBC [18]. Although red blood cell indices in dogs are commonly used, platelet indices are less commonly used [39]. Aside from the present platelet count and mean platelet volume, various other factors about platelets may be assessed [34]. Platelet indices (PI) are measures that indicate the activity of platelets [31]. Blood-based platelet parameters appear to be promising new biomarkers of numerous disorders, both acute and chronic, due to their relatively easy accessibility and low-cost assessment techniques [31].

Platelet indices have been investigated in many diseases [10,14,15,18,19,22,23,26,39,42,44] in dogs. However, there is no information about the availability of PLT and its indices in routine practice in dogs with TVT. The aim of the presented study was to determine the usefulness of total PLT measurement and PLT indices in bitches with TVT, as well as examine the relationship between white blood cells, RBC, PLT, MPV, PDW, PCT, and MPV/PLT.

MATERIALS AND METHODS

Animals

Forty-two bitches of various breeds were included in the study. The study group consisted of 23 bitches with TVT. The control group consisted of 19 clinically and gynecologically healthy ones. Metastasis was not observed in any of the animals involved in the study.

Clinical and cytological examination

History, clinical findings and cytological examinations were evaluated for the diagnosis of cTVT. In bitches with hemorrhagic discharge and neoplastic lesions, vaginal cytological examination was performed. For the cytological examination, a smear was prepared from a non-sterile swab sample taken from the tumor tissue in the vagina. The smears were kept in methanol for 3 min, then they were stained by keeping them in 1:1 diluted May-Grünwald solution[1] for 5 min and 3:1 diluted Giemsa solution[1] for 10 min, and they were washed with distilled water [29]. Typical TVT cells with large nuclei and intracytoplasmic vacuoles were observed in the vaginal cytological examinations of bitches, and the diagnosis of TVT was made [8].

Sample collection and laboratory methods

Venous blood samples were obtained by cephalic venipuncture into tubes containing K3EDTA[2]. Collected blood samples were analyzed using an automated hematology analyzer[3]. As a result of the analysis, WBC, RBC, HGB, HCT, MCV, MCHC, RDW, PLT, MPV, PDW, PCT, and MPV/PLT data were obtained.

Statistical analysis

Descriptive statistics were shown as mean ± standard deviation for continuous variables. The normality assumption was checked with Shapiro Wilk Test. The difference between healthy bitches and those with TVT in complete blood count parameters was determined with Independent Samples *t* test if the normality assumption was held or Mann Whitney-U Test if the normality assumption was not held. The accuracy of the potential complete blood count parameters in predicting the existence of TVT was estimated with Receiver Operating Characteristic (ROC) analysis by calculating AUC (area under curve) and 95% confidence intervals. The optimal cut-off point maximizing the Youden's J statistic of each parameter to predict the existence of TVT was determined [J= max (sensitivity+specificity-1)]. The relationships between complete blood count parameters in healthy bitches and those with TVT were specified with Pearson Correlation Coefficient if the normality assumption was hold or Spearman's Rank Correlation Coefficient if the normality assumption was not hold. A P value < 0.05 was considered statistically significant. All statistical analysis were performed using SPSS Statistics for Windows, Version 23.0[4].

RESULTS

The breeds included in the study are given in Table 1. Healthy bitches were 39.16 ± 5.37 months old, while TVT bitches were 47.61 ± 5.14 months old. Typical TVT cells with large nuclei and intracytoplasmic vacuoles were observed in microscopic examinations (40x) of vaginal smear samples prepared for diagnosis from animals with TVT. When the CBC analyses of healthy bitches and those with TVT were examined, it was determined that mild leukocytosis, an increase in PLT, and a decrease in MCV and MPV/PLT were observed in bitches with TVT compared to healthy bitches (Table 2). Even though an increase in platelet count of bitches with TVT was detected in hematological analysis ($P = 0.020$), it was ranged within the reference values [11].

As significant differences were detected in WBC, MCV, PLT, and MPV/PLT values in bitches with TVT, the diagnostic predictability of all 4 parameters for TVT was examined by ROC analysis (Figure 1). The highest significant AUC value was obtained for WBC (AUC = 0.867), MCV (AUC = 0.761), followed by PLT (AUC = 0.711). The AUC value obtained for the MPV/PLT ratio was statistically significant but relatively weak (AUC = 0.696). Cut-off values in the complete blood count of bitches with TVT were determined as WBC: 13.35 (sensitivity: 78%; specificity: 90%); MCV: 67 (sensitivity: 57%; specificity: 95%); PLT: 315.50 (sensitivity: 65%; specificity: 74%); and MPV/PLT: 0.028 (sensitivity: 78%; specificity: 58%) [Table 3].

A correlation analysis was performed to evaluate the relationship between the blood parameters measured in both groups. In CBC of healthy bitches, there was a strong positive correlation between RBC and HCT and HGB; a strong positive correlation between HGB and HCT; a slight negative correlation between MPV and MPV/PLT; a slight negative correlation between WBC and MPV/PLT; a slight negative correlation between MCHC and RDW; a strong negative correlation between PLT and MPV/PLT; and a moderate negative correlation between PCT and MPV/PLT (Table 4). In the CBC of bitches with TVT, it was detected that there was a moderately positive correlation between RBC and HGB; a strongly positive correlation between RBC and HCT; a strongly positive correlation between HGB and HCT; a mildly positive correlation between HGB and MCV and MCHC; a mildly positive correlation between HCT and MCV, a moderately positive correlation between RDW and PDW; a strongly positive correlation between PLT and PCT; a slightly negative correlation between MCV and RDW; a slightly negative correlation between MCHC and MPV/PLT; a strongly negative correlation between PLT and MPV/PLT; and a strongly negative correlation between PCT and MPV/PLT (Table 5).

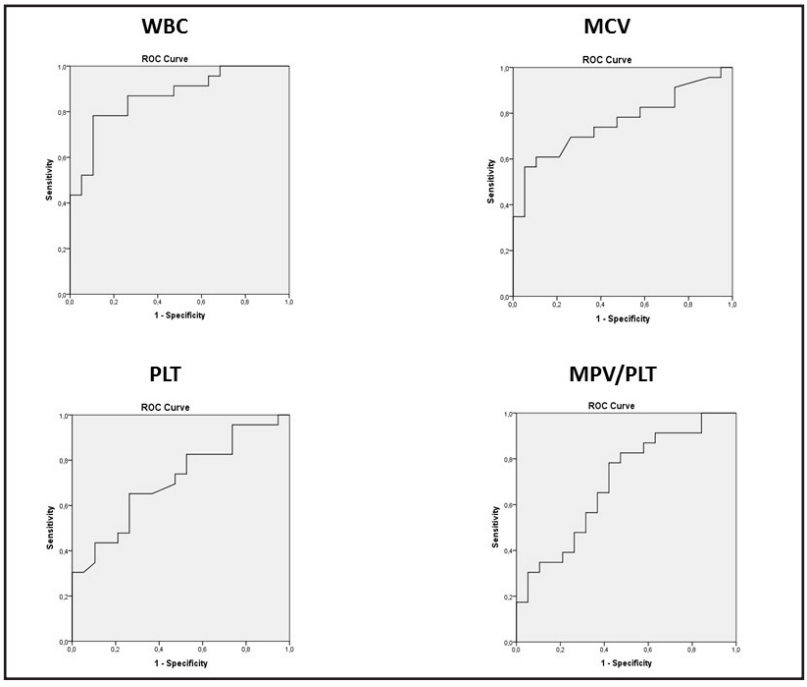

Figure 1. ROC curves of WBC, MCV, PLT, and MPV/PLT in bitches with TVT.

Table 1. The breeds of bitches involved in the study.

Breed	Healthy (n = 19)	TVT (n = 23)
Golden Retriever	1	4
Terrier	3	0
Siberian Husky	1	2
Mix	2	9
Pointer	2	0
Belgian Malinois	3	0
King Charles Spaniel	1	0
Doberman Pincher	1	0
German Sheephard	4	2
Labrador Retriever	1	0
Turkish Sheephard (Kangal)	0	3
Boxer	0	1
Papillion	0	1
American Terrier	0	1

Table 2. Complete blood count results of 42 bitches of both groups of this study.

Parameter	Diagnosis		*P*
	Healthy (n = 19) Mean ± SD	TVT (n = 23) Mean ± SD	
WBC × 10^3/µL	10.64 ± 2.58	17.04 ± 7.56	< 0.001[1]
RBC × 10^6/µL	6.92 ± 0.90	7.29 ± 1.16	0.266[2]
HGB g/dL	14.36 ± 1.94	14.12 ± 2.78	0.759[2]
HCT %	48.33 ± 6.28	47.87 ± 8.82	0.850[2]
MCV fL	69.91 ± 2.64	65.67 ± 5.47	0.002[2]
MCHC g/dL	29.65 ± 0.58	29.63 ± 3.04	0.704[1]
RDW %	14.13 ± 1.09	15.26 ± 3.21	0.125[2]
PLT × 10^3/µL	305.32 ± 72.29	415.27 ± 163.19	0.020[1]
MPV fL	8.39 ± 0.95	8.70 ± 0.90	0.278[2]
PDW %	15.93 ± 0.36	17.08 ± 7.25	0.790[1]
PCT	0.26 ± 0.06	0.35 ± 0.16	0.066[1]
MPV/PLT	0.03 ± 0.01	0.02 ± 0.01	0.026[2]

[1]Mann Whitney U Test; [2]Independent Samples *t* Test.

Table 3. AUC results for complete blood count parameters obtained from bitches with TVT.

Parameter	AUC (95% CI)	Cut - off	Sensitivity	Specificity	*P* - value
WBC × 10^3/µL	0.867 (0.759 - 0.976)	13.35	0.783	0.895	< 0.001
RBC × 10^6/µL	0.621 (0.451 - 0.791)	7.95	0.348	0.947	0.180
HGB g/dL	0.538 (0.361 - 0.714)	11.95	0.348	0.895	0.677
HCT %	0.516 (0.338 - 0.694)	39.35	0.261	0.947	0.860
MCV fL	0.761 (0.615 - 0.907)	67.00	0.565	0.947	0.004
MCHC g/dL	0.534 (0.348 - 0.721)	28.85	0.348	1.000	0.705
RDW %	0.598 (0.432 - 0.774)	15.65	0.391	0.947	0.277
PLT × 10^3/µL	0.711 (0.555 - 0.866)	315.50	0.652	0.737	0.020
MPV fL	0.566 (0.386 - 0.747)	8.35	0.696	0.526	0.464
PDW %	0.524 (0.345 - 0.703)	15.95	0.565	0.684	0.791
PCT	0.666 (0.501 - 0.831)	0.35	0.435	0.947	0.067
MPV/PLT	0.696 (0.535 - 0.856)	0.028	0.783	0.579	0.031

Table 4. Correlation between CBC parameters in healthy bitches (n = 19).

Parameter	WBC	RBC	HGB	HCT	MCV	MCHC	RDW	PLT	MPV	PDW	PCT	MPV/PLT
WBC	1*	-0.367*	-0.384*	-0.404*	0.155*	0.021*	-0.192*	0.411*	-0.294*	0.224*	0.256*	**-0.492***
RBC		1*	**0.946***	**0.956***	-0.142*	0.198*	-0.161*	-0.311*	0.147*	-0.162*	-0.251*	0.297*
HGB			1*	**0.989***	0.151*	0.346*	-0.315*	-0.306*	0.109*	-0.132*	-0.261*	0.291*
HCT				1*	0.153*	0.205*	-0.262*	-0.268*	0.314*	-0.132*	-0.211*	0.272*
MCV					1*	0.039*	-0.377*	0.148*	-0.020*	0.100*	-0.212*	-0.084*
MCHC						1*	**-0.465***	-0.323*	-0.138*	-0.023*	-0.213*	0.193*
RDW							1*	-0.251*	0.287*	0.445*	-0.214*	0.341*
PLT								1*	-0.321*	-0.066*	-0.215*	**-0.904***
MPV									1*	0.024*	-0.216*	**0.639***
PDW										1*	-0.217*	0.106*
PCT											-0.218*	**-0.617***
MPV/PLT												1*

Statistically significant correlation coefficients are shown as bold. *Pearson Correlation Coefficient; **Spearman Correlation Coefficient.

Table 5. Correlation between CBC parameters in bitches with TVT (n = 23).

Parameter	WBC	RBC	HGB	HCT	MCV	MCHC	RDW	PLT	MPV	PDW	PCT	MPV/PLT
WBC	1**	0.123**	-0.042**	0.048**	0.200**	-0.353**	0.222**	0.016**	0.110**	0.032**	0.068**	0.045**
RBC		1*	**0.674***	**0.890***	-0.004*	-0.246*	0.146*	-0.138*	-0.249*	-0.075*	-0.164*	0.136*
HGB			1*	**0.809***	**0.433***	**0.417***	-0.230*	0.133*	-0.137*	-0.036*	0.084*	-0.179*
HCT				1*	**0.448***	-0.189*	-0.122*	-0.077*	-0.118*	-0.112*	-0.101*	0.044*
MCV					1*	0.037*	**-0.494***	0.149*	0.252*	-0.078*	0.153*	-0.195*
MCHC						1**	-0.299**	0.359**	-0.030**	0.089**	0.258**	**-0.497****
RDW							1*	0.121*	0.011*	**0.512***	0.180*	-0.005*
PLT								1**	0.378**	0.128**	**0.947****	**-0.939****
MPV									1*	0.259*	0.306*	0.002*
PDW										1**	0.194**	-0.084**
PCT											1**	**-0.899****
MPV/PLT												1*

Statistically significant correlation coefficients are shown as bold. *Pearson Correlation Coefficient; **Spearman Correlation Coefficient.

DISCUSSION

Veterinary oncology is an area of small animal medicine that is continually evolving [17,27]. In this field, canine transmissable venereal tumor is a commonly encountered neoplastic disorder in both pet and stray dogs [20]. Even though cTVT has been predominantly observed in mixed-breed dogs, it is stated that cTVT can also be observed in purebred dogs [30]. The current study found that cTVT incidence was similar in purebred and mixed breed bitches (Table 1). Although canine transmissible venereal tumor can be seen in dogs of all ages, it tends to be more common in young dogs, aged 2-7 years [8,12,28,32]. Consistent with previous studies, the average age of the bitches diagnosed with TVT in this study was 47.61 ± 5.14 months.

Mating is addressed for the major transmission route of this tumor [1]. The tumor typically spreads during mating due to significant abrasion and bleeding of the vaginal and penile mucosa, leading for convenient tumor transmission [1]. Tumor may rarely spread to other organs, including the mouth, nose, skin, and eyes [4,35,43], in addition to the external genital organs in both sexes [2,32]. Once cTVT develops, the major clinical symptom is hemorrhagic discharge from the genital organ, and the other common symptom is deformation of the external genital organ [13]. The diagnosis of cTVT is based on its clinical appearance, supported by cytological examination and the observation of characteristic tumor cells [8]. In many studies, hematological analysis, including CBC or biochemistry, was used for either the evaluation of the response to the chemotherapy or the investigation of the effects of chemotherapeutics in dogs with TVT [5,8,32].

Hematological analysis as a complementary diagnostic or prognostic tool is commonly used in veterinary practice [25,41]. A complete blood count conducted by auto-analyzers provides a specification of the blood cells and a determination of cell volume or size [34]. Hence, one of the most popular laboratory procedures, CBC, may simply analyze different cell types [18]. Thanks to the discrimination of cell types, panels including RBC, WBC or platelet indices of CBC are used for the diagnosis or monitoring of many diseases [10,18,19,39,42]. In several studies, RBC and WBC indices were evaluated for the monitoring of the effects of chemotherapy in dogs with TVT [5,8]. Even though hemorrhagic discharge occurs, the hematocrit value ranges within the reference levels in many cTVT cases [5,8,12]. The RBC indices [RBC indices: mean erythrocyte volume (MCV), mean erythrocyte hemoglobin (MCH), mean erythrocyte hemoglobin concentration (MHC), and erythrocyte distribution width (RDW)] was also ranged within the reference levels in this study, as in previous studies. WBCs play an important role in systemic inflammatory response as well as tumor development and metastatic processes [15,24]. Leukocytosis related to mammary tumors in dogs is reported [15]. On the other hand, approximately a quarter of cTVT cases have mild to moderate leukocytosis, which is also reported [20]. Mild leukocytosis was also observed in bitches with TVT in this study, which is consistent with previous studies [5,8,12]. Hereby, this may be related to the active inflammatory process of tumor and a tendency toward the secondary bacterial infection caused by tumoral tissue.

Contrary to other indices, including WBC and RBC, the platelet indices are not used very often in daily clinical practice [39]. But, platelet indices (PI), often known as indicators of platelet activity, are values acquired as part of a daily blood count. Mean platelet volume (MPV), platelet distribution width (PDW), platelet cell ratio (PCR), and plateletcrit (PCT) are the most often examined PIs [6,31]. Mean platelet volume (MPV), a measure of platelet size; platelet distribution width (PDW), an indication of platelet size fluctuation; and plateletcrit (PCT), the blood volume mass of platelets, are the most routinely assessed PIs. Platelet structure and proliferation kinetics are linked to PI [23]. PIs were used to evaluate many diseases (including endotoxemia, chronic enteropathy, mammary tumor, parvoviral enteritis, septic peritonitis, lymphoma, pyometra, visceral leishmaniasis, babesiosis, etc.) in terms of either diagnosis or prognosis [10,14,15,18,19,23,39,42,44]. Even though there are many studies including hemato-biochemical analysis in cTVT [3,5,21,32], there is no information available for either diagnostic or prognostic usage of the platelet indices in this neoplastic disease.

Platelets are megakaryocyte cells found in the bone marrow [22]. They have the biggest cell population after erythrocytes and participate in coagulation [18]. Platelets are the most critical cells in hemostasis, but they are also involved in thrombosis, inflammation, and neoplasia. Platelets circulate in

the bloodstream for an average of 7-9 days before being eliminated from circulation by macrophages in the spleen and liver. In healthy animals, platelet count remains steady [22]. Platelets (PLTs) also play a significant role in inflammation, which is critical in tumor growth and metastasis [36]. Thrombocytosis is described as an increase in platelet count in peripheral blood over the reference range specified for that species, and it can be primary or secondary [33]. While primary thrombocytosis is a myeloproliferative disorder characterized by excessive platelet production, secondary or "reactive" thrombocytosis, depending on the etiology, can be temporary or permanent [33,37]. It is stated that neoplasia is the most prevalent cause of secondary thrombocytosis in dogs [16,33]. In a study conducted in patients with bone tumors in human medicine, it was reported that the mean PLT value of the tumor patients was substantially greater than that of the controls [36]. On the other hand, bitches with grade 3 mammary tumors had a higher PLT level in their CBC, but it ranged within the reference levels [15]. Consistent with the literature, in the current study, the platelet count in bitches with TVT was higher than in healthy bitches but ranged within the reference values. So, this may be interpreted as an activation of platelets by the inflammatory process of the tumor, in addition to homeostasis role of platelets.

The mean platelet volume (MPV) represents platelet size, which is associated with platelet formation and activation [40]. The mean platelet volume (MPV) is an index of PLT volume, and there are different perspectives on how to reduce MPV in neoplastic processes. According to one of them, the tumor-associated inflammatory state causes an increase in PLT consumption and, as a result, a decrease in MPV [36]. An MPV/PLT ratio (MPR) has recently been presented as a novel inflammatory predictor and a sign of a poor prognosis [9]. It was discovered that the MPV/PLT ratio decreased in tumor patients compared to controls [36]. The MPV/PLT ratio is reduced in esophageal cancer patients [38] as well as in those with colorectal cancer [40]. Even though there are various studies reporting a decrease in the MPV/PLT ratio in neoplastic diseases [36,38,40], literature exists about an increase in the MPV/PLT ratio in some neoplastic diseases, such as hepatic cell carcinoma [7]. Contrary to Cho et al. [7] and similar to previous studies [36,38,40], the MPV/PLT ratio in this study was found lower in bitches with cTVT (Table 2). Related to the strong negative correlation between PLT and MPV/PLT detected in this study, tumor-induced platelet increase may have decreased the MPV/PLT ratio in bitches with TVT (Table 2). Hereby, this may be related to the inflammatory process of the tumor tissue. Our ROC analysis also showed that the MPV/PLT ratio (cutoff value < 0.028) can be used as a remarkable laboratory marker for bitches with cTVT, with 78% sensitivity and 58% specificity.

CONCLUSIONS

Finally, in canine transmissible venereal tumor cases, platelet indices, especially PLT and the MPV/PLT ratio, seem to be notable laboratory markers in terms of easy accessibility and low-cost assessment techniques. However, new evidences regarding its utility as a diagnostic or prognostic marker in canine transmissible venereal tumors should be established through comprehensive further research having larger sample size.

MANUFACTURERS

[1]Merck KGaA. Darmstadt, Germany.

[2]Becton Dickinson (BD). Franklin Lakes, NJ, USA.

[3]Melet Schloesing Laboratoires. Osny, France.

[4]IBM - International Business Machines Corporation. Armonk, NY, USA.

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***Ethical approval*.** The Hatay Mustafa Kemal University Animal Experiments Local Ethics Committee proved ethical approval with decision number 2022/07-06. Besides, the informed consent (either verbal or written) was obtained from the owner(s) of all animal(s) described in this work for the scientific studies. Also, no animals or humans are identifiable within this publication, and, therefore, additional informed consent for publication was not required.

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