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Diagnostic and prognostic significance of platelet large cell count and ratio in cats across stages of hypertrophic cardiomyopathy

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the most common cardiac disease in cats and a major predisposing factor for arterial thromboembolism (ATE), a life-threatening complication. While platelet activation plays a pivotal role in thrombogenesis, the diagnostic and prognostic value of novel platelet-derived indices such as platelet-large cell count (PLCC) and platelet-large cell ratio (PLCR) remains poorly defined in feline patients. This study aimed to assess PLCC and PLCR across different stages of HCM and to evaluate their potential as biomarkers for thrombotic risk. Seventy-one client-owned cats were categorized based on the ACVIM guidelines into healthy controls (Stage A), asymptomatic HCM (Stage B), symptomatic HCM (Stage C/D), and HCM with ATE. PLCC was elevated ($P < 0.01$) in cats with HCM compared to controls, while PLCR showed a stepwise increase from Stage A to Stage C/D ($P < 0.01$). PLCC was reduced in cats with ATE ($P < 0.05$). A negative relationship was observed between platelet count and PLCR. However, a positive correlation was found between PLCC, platelet distribution width, and WBC count ($P < 0.05$). ROC curve analysis demonstrated optimal thresholds of PLCC $>69 \times 10^9$/L and PLCR ≤ 74 % for predicting ATE. Also, an Extreme Gradient Boost-based machine learning model was applied to predict FATE risk with SHAP (SHapley Additive exPlanations) analysis for model interpretation. The model demonstrated moderate discriminative ability (AUC-ROC = 0.68), with PLCC identified as the strongest predictor and PLCR as a contextual cofactor. These findings suggest that PLCC and PLCR may serve as informative adjunctive hematological parameters for assessing disease severity and stratifying thromboembolic risk in cats with HCM.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common cardiac disease in domestic cats, characterized by concentric left ventricular (LV) hypertrophy in the absence of systemic hypertension, hyperthyroidism, or other identifiable secondary causes of myocardial thickening (Ware and Ward, 2019; Payne et al., 2015; Gaia de Sousa et al., 2025). Feline hypertrophic cardiomyopathy (fHCM) exhibits a broad spectrum of clinical manifestations, ranging from asymptomatic cases to congestive heart failure (CHF), arterial thromboembolism (ATE or FATE), cardiac arrhythmias, and sudden death (Borgeat et al., 2014; Ware and Ward, 2019; Bakirel et al., 2021; Kittleson and Côté, 2021a; Kocatürk et al., 2023a). Among these complications, FATE is particularly devastating, associated with a sudden onset, severe pain, high recurrence rate, and poor long-term survival despite intensive medical management (Smith et al., 2003; Luis Fuentes, 2012; Luis Fuentes et al., 2020; Ware and Ward, 2019).

Platelet activation and thrombogenesis are central to the pathogenesis of fHCM (Luis Fuentes, 2012; Tablin et al., 2014; Kocatürk et al., 2023b). In human and veterinary medicine, platelet-derived indices have gained interest as biomarkers of thrombotic activity and disease severity. Conventional indices such as mean platelet volume (MPV) and platelet distribution width (PDW) have shown promise in cardiovascular and inflammatory diseases in humans (Chu et al., 2010; Garcia-Pachon et al., 2020; Kandis et al., 2011; Korniluk et al., 2019; Sloan et al., 2015; Yuri Gasparyan et al., 2011), and cats (Çolakoğlu et al., 2018; Johnson et al., 2024; Kocatürk et al., 2023b). More recently, attention has shifted to advanced platelet parameters, such as platelet large cell count (PLCC) and platelet large cell ratio (PLCR), which reflect the absolute and relative presence of large, metabolically active platelets with enhanced prothrombotic potential (Khandekar et al., 2006). In human medicine, these indices have demonstrated diagnostic and prognostic utility across

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diverse conditions, such as myelodysplastic syndrome (Chen et al., 2022), COVID-19 (Çelik et al., 2024; Sugihara et al., 2024), immune thrombocytopenia (Kaito et al., 2005), cancer (Anand and Raju, 2024), and coronary artery diseases (Batista et al., 2018; Venkataswamy Reddy et al., 2024).

Despite this growing body of evidence, the clinical application of PLCC and PLCR in veterinary cardiology, particularly in fHCM, remains limited. Understanding their role in thrombogenesis could enhance early risk stratification and support treatment decision-making, especially given its accessibility via standard automated hematology analyzers. Recent studies have begun to explore hematologic changes associated with fHCM and FATE (Çolakoğlu et al., 2018; Johnson et al., 2024; Kocatürk et al., 2023a), but the predictive value of advanced platelet indices for thromboembolic risk has yet to be clearly established.

Accordingly, this study aimed to: (1) evaluate the diagnostic and prognostic relevance of PLCC and PLCR in fHCM; (2) assess their association with clinical disease staging according to the American College of Veterinary Internal Medicine (ACVIM) consensus classification (Luis Fuentes et al., 2020); and (3) determine their predictive value for the development of FATE. We hypothesize that cats with FATE will exhibit distinct platelet profiles compared with those with uncomplicated HCM. PLCC and PLCR may serve as accessible hematologic biomarkers to aid in risk stratification and clinical management.

2. Materials and methods

A retrospective observational study was conducted by reviewing the medical records of cats evaluated by the author (ZY) at the cardiology unit of the Animal Teaching Hospital, Bursa Uludağ University, and in private clinics where official consultancy services were provided. The study involved only a retrospective review of anonymized medical records obtained during routine clinical care. This retrospective study was approved by the institutional ethics committee at Bursa Uludag University (ID: 2025–09/08).

2.1. Study population

A total of 71 client-owned cats of various breeds, sexes, ages, and body weights were included in the study. Of these, 10 cats served as healthy controls without structural heart disease (Stage A), and 50 cats were diagnosed with HCM at various clinical stages (Stages B through D). An additional 11 cats had HCM complicated by confirmed FATE (Table 1). Cats diagnosed with FATE were included as a separate study group. The diagnosis of FATE was established based on clinical examination and echocardiographic evaluation. Physical examination followed the “5P rule,” which characterizes the typical presenting signs of pallor (pale or cyanotic digits), polar/poikilothermy (cold extremities), pulselessness, paresis/paralysis, and pain. Diagnostic confirmation was supported by the absence of femoral arterial pulses in the affected limb (s) and echocardiographic evidence of a thrombus and/or spontaneous echo-contrast (“smoke” appearance) in the left atrium or left atrial appendage. Stage C and D HCM patients were selected from cats with no history of FATE and without any “5P” clinical signs at the time of inclusion. Therefore, due to their distinct clinical presentations, FATE cases and Stage C/D HCM patients were analyzed as separate groups in this study.

The 50 cats with HCM and no ATE were further staged according to the ACVIM consensus guidelines (Fuentes, 2012) as follows: Stage B1 ($n = 10$), Stage B2 ($n = 11$), Stage C ($n = 17$), and Stage D ($n = 12$). Clinical data were obtained from two sources: 33 cats were evaluated at the Cardiology Unit of the Animal Teaching Hospital, Bursa Uludağ University, and 38 cats were assessed in private veterinary clinics where the author (ZY) provided cardiology consultancy services.

A comprehensive clinical assessment was performed for each cat, including detailed physical examination, thoracic radiography, electrocardiogram, transthoracic echocardiography, and standard laboratory testing. The laboratory workup included a complete blood count (CBC) and a biochemical profile (serum cardiac and hepato-renal injury markers and electrolytes).

Cats were enrolled based on the following criteria: (1) a diagnosis of HCM confirmed by echocardiography; (2) a diagnosis of ATE secondary to HCM confirmed by echocardiography or CT angiography; and (3) availability of diagnostic and laboratory records sufficient to assess PLCR and PLCC.

Healthy control cats (Stage A) were retrospectively selected from hospital records of the cats presented to the clinic for routine vaccination. At the owners’ request, these cats had undergone a comprehensive health screening, including CBC and a detailed cardiologic evaluation. Only those with no clinical, hematological, or echocardiographic abnormalities were included in the control group.

2.2. Clinical classification of HCM

fHCM was staged according to the guidelines of the ACVIM

Table 1
Demographic and Echocardiographic Characteristics of Cats Grouped by ACVIM Stage and FATE Status.

ACVIM Stage	A	B1	B2	C	D	FATE	*P* value
Sample size	10	10	11	17	12	11	NS
Sex (F/M)	5/5	4/6	6/5	7/10	6/7	4/7	NS
Age (year)	5.3 ± 2.9	5.1 ± 1.8	7.3 ± 4.4	7.3 ± 3.4	5.4 ± 3.9	6.6 ± 5.3	NS
Weight (kg)	4.5 ± 1.1	4.6 ± 0.9	5.4 ± 0.8	5.1 ± 0.3	4.1 ± 0.8	5.1 ± 0.9	NS
Breed							
BSH	3	2	3	7	4	2	
BLH	2	2	1	1	2	2	
Scottish Fold	2	3	3	3	4	4	
Siamese	1	1	1	0	0	0	
Angora cat	0	0	2	0	0	0	
Persian	0	0	1	1	0	1	
Mixed	2	2	0	5	2	2	
Echocardiography (M-Mode)							
HR bpm	179 ± 25	181 ± 33	187 ± 19	218 ± 52	234 ± 16	209 ± 27	NS
IVSd (mm)	3.9 ± 0.9^{a}	5.2 ± 1.5^{ab}	5.9 ± 1.6^{ab}	6.4 ± 0.6^{ab}	9.0 ± 2.4^{b}	6.7 ± 1.5^{ab}	<0.05
IVSs (mm)	5.6 ± 1.3	8.3 ± 1.7	7.7 ± 0.4	8.2 ± 0.3	9.3 ± 2.7	7.9 ± 0.3	NS
LVIDd (mm)	12.2 ± 2.3	15.2 ± 1.7	13.5 ± 1.4	12.3 ± 2.4	13.1 ± 3.3	12.3 ± 2.6	NS
LVIDs (mm)	6.8 ± 0.8	7.8 ± 2.7	7.7 ± 0.4	6.0 ± 2.3	8.4 ± 1.7	7.9 ± 2.5	NS
LVFWd (mm)	4.6 ± 0.7	6.7 ± 2.0	7.2 ± 0.6	7.6 ± 1.0	8.0 ± 1.0	7.1 ± 2.4	NS
LVFWs (mm)	6.7 ± 1.1	9.4 ± 2.0	8.8 ± 0.7	9.2 ± 1.1	9.0 ± 1.7	8.5 ± 1.5	NS
LAd (mm)	10.0 ± 2.9^{a}	13.2 ± 0.9^{ab}	14.3 ± 3.0^{ab}	17.3 ± 3.2^{ab}	22.0 ± 9.5^{b}	18.0 ± 2.6^{ab}	<0.05
LA/Ao ratio	1.0 ± 0.1^{a}	1.4 ± 0.3^{ab}	1.7 ± 0.3^{ab}	1.8 ± 0.3^{b}	2.8 ± 1.3^{b}	2.2 ± 0.3^{ab}	<0.05
LAV_{max} (mL)	1.0 ± 0.0 ^{a}	1.8 ± 0.8 ^{a}	2.3 ± 1.5^{ab}	2.5 ± 1.3^{ab}	7.6 ± 4.2^{6}	5.3 ± 2.0^{b}	<0.01

ACVIM: The American College of Veterinary Internal Medicine Consensus Guidelines (Luis Fuentes et al., 2020), FATE Feline Arterial Thromboembolism, BSH British Shorthair, BLH British Longhair; LVIDd Left ventricular internal diameter in diastole, IVSd Interventricular septum thickness in diastole, LVFWd Left ventricular free wall thickness in diastole, LAD Left atrial diameter, LA/Ao Left atrium to aortic diameter ratio, and LAV_{max} Left atrial maximal volume (Apical 4ch view). There are statistically significant differences between the values marked with different letters. NS Not Significant.

consensus statement (Luis Fuentes et al., 2020), using a combination of echocardiographic findings and clinical presentation:

Stage A: Clinically healthy cats are considered at risk for developing HCM but have no echocardiographic evidence of structural heart disease.

Stage B1: Cats with mild structural changes, including normal or mildly enlarged left atrium (LA) and mild thickening of the interventricular septum (IVS) and/or left ventricular (LV) free wall, in the absence of clinical signs.

Stage B2: Cats with moderate to marked LA enlargement and moderate to severe LV wall thickening, without clinical signs of heart disease.

Stage C: Cats presenting with clinical signs of CHF attributable to HCM.

Stage D: Cats with advanced or refractory CHF are poorly responsive to standard medical management.

For this study, Stage A cats served as the healthy control group. Stages B1 and B2 were grouped as asymptomatic HCM, whereas Stages C and D were grouped as symptomatic HCM. Cats with HCM and confirmed FATE were analyzed separately from those with uncomplicated HCM (see Table 1).

2.3. Inclusion and exclusion criteria

Cats were included in the study if they met the following criteria: age greater than one year; a diagnosis of HCM confirmed by echocardiographic examination; and the availability of a CBC, including PLCC and PLCR. In cases of hypertrophic obstructive cardiomyopathy (HOCM), defined as HCM with dynamic left ventricular outflow tract obstruction (LVOTO), inclusion required an aortic peak velocity (Vmax) exceeding 2.5 m/s. LVOTO was diagnosed based on a dynamic narrowing of the LV outflow tract during systole, associated with elevated flow velocities through the aortic valve. Notably, HOCM was not excluded from the study and was considered a clinically relevant subtype of HCM (Saito et al., 2025).

For cats with suspected FATE, additional inclusion criteria were the presence of spontaneous echocardiographic contrast ("smoke") or visible LA thrombus on echocardiography combined with clinical signs consistent with FATE (Borgeat et al., 2014; Smith et al., 2003).

Exclusion criteria included any concurrent systemic, infectious, or metabolic conditions that could confound the interpretation of platelet indices. These included positive status for feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), or feline coronavirus (FeCoV), as well as diagnosed endocrine or metabolic disorders such as hyperthyroidism or diabetes mellitus. Additional exclusion criteria were obesity or cachexia, moderate to severe dehydration, and recent (within the past three weeks) administration of medications known to alter platelet function (e.g., anticoagulants or antiplatelet agents). Cats in Stage D receiving ongoing cardiac therapy were exempted from the pharmacological exclusion criterion on clinical grounds. Cats lacking CBC data were also excluded from the analysis.

2.4. Treatment of stage D

In Stage D HCM cats, pharmacologic therapy was permitted to manage advanced (refractory) heart failure. In these patients, diuretic therapy primarily consisted of high-dose furosemide (2–6 mg/kg/day PO), administered alone or, if necessary, in combination with torsemide (0.1–0.2 mg/kg/day PO), to relieve pulmonary edema, pleural effusion, and congestion. ACE inhibitors such as enalapril or benazepril (0.25–0.5 mg/kg PO q12–24 h) were administered to reduce afterload and limit cardiac remodeling, while beta-blockers (e.g., atenolol 6.25–12.5 mg/kg PO q12h) were used to control tachycardia and decrease pressure gradient across the aortic outflow in case of left ventricular outflow tract obstruction. In cats with HCM-related congestive heart failure, pimobendan (0.25–0.3 mg/kg PO q12h) was administered for positive inotropic support. Its use was guided by evidence of systolic dysfunction, assessed by left ventricular fractional shortening (LV FS), ejection fraction (EF), and global longitudinal strain. Supportive measures, including oxygen therapy, sodium restriction, and careful fluid balance monitoring, were also implemented, and medication selection and dosing were individualized based on clinical response and renal function. Clopidogrel (18.75 mg/cat PO q24h) is currently the standard antiplatelet agent for the prevention of initial and recurrent ATE in cats. Because they are prone to congestive heart failure, Stage D patients were considered at high risk for ATE. To reduce the risk of thromboembolism, anticoagulants such as low-molecular-weight heparins (e.g., enoxaparin, 0.75–1 mg/kg subcutaneously every 6 to 12 h) and selective factor Xa inhibitors (e.g., rivaroxaban, 0.5–1 mg/kg orally every 24 h; apixaban, 0.625 mg/cat orally every 12 h) (Kittleson and Côté, 2021b; Luis Fuentes et al., 2020) were administered, often in combination with antiplatelet agents to enhance prophylactic efficacy.

2.5. Clinical diagnosis and staging of HCM

The diagnosis and clinical staging of HCM were performed following the consensus guidelines of the ACVIM (Luis Fuentes et al., 2020). This process integrated clinical history, thoracic radiographic findings, electrocardiograms, and a comprehensive transthoracic echocardiographic assessment. Echocardiographic examinations were conducted using either the Vivid S60 Ultra Edition (GE HealthCare, Norway) or the Vetus9 (Mindray, China). The echocardiographic examinations were performed by the primary authors (ZY or JK) or by co-authors (DA and TV) under the direct supervision of the primary investigators.

Standard echocardiographic techniques included two-dimensional (2D), M-mode, color Doppler, continuous-wave (CW), and pulsed-wave (PW) Doppler imaging. Image acquisition was performed from standard imaging windows, including the right parasternal short-axis (RPSAx) and long-axis (RPLAx), subcostal views, and left apical two-, three-, and four-chamber views. LV wall thickness was evaluated using a segmental approach in RPSAx and RPLAx echocardiographic views. During end-diastole, the myocardium was scrutinized at all levels, from the basal to the apical segments. A segment was classified as hypertrophied if $\geq$50 % of its length exhibited a wall thickness of $\geq$6 mm, measured perpendicular to the endocardial border. This criterion was applied to distinguish pathological hypertrophy from focal or artefactual thickening and ensure consistent HCM classification across varying myocardial distribution patterns (De Madron et al., 2016; Granström et al., 2011).

Left atrial (LA) size was assessed using the area-length method based on biplane images acquired from the left apical two- and four-chamber views. Measurements were performed at end-systole, and LA enlargement was defined according to established cut-off values for the LA area and indexed volume. Additionally, the LA/Ao ratio was measured from the RPSAx view at the aortic valve level using manual caliper placement and ECG guidance; a ratio $>$ 1.5 indicated LA enlargement (see Table 1). A volumetric assessment of the LA was performed using the area-length method from the A4C (De Madron et al., 2016).

Left ventricular outflow tract (LVOT) and aortic flow velocities were assessed using the apical five-chamber and subcostal views. A peak systolic aortic velocity exceeding 2.5 m/s was interpreted as consistent with dynamic LVOTO (Saito et al., 2025), supporting a diagnosis of HOCM, as mentioned above.

In routine echocardiographic examinations, we also evaluated systolic and diastolic heart function using spectral Doppler analysis, tissue Doppler imaging (TDI), and two-dimensional speckle tracking echocardiography (2D STE); however, the results of these evaluations were not included in this study.

2.6. Hematological analysis

Peripheral blood samples were collected from all cats during

diagnosis as part of the routine clinical evaluation. A CBC was performed using an automated hematology analyzer that determines differential leukocytes and PLT counts using laser flow and impedance methods, respectively (VH5R, HasVet, Türkiye). The following platelet-related parameters were specifically recorded for analysis: platelet count, MPV, plateletcrit (PCT), PDW, PLCC, and PLCR.

PLCC was defined as the absolute number of platelets with a volume exceeding 12 femtoliters (fL), as calculated by the analyzer based on size-specific detection thresholds. PLCR was expressed as the percentage of large platelets relative to the total platelet count, serving as a surrogate marker for platelet activation and turnover.

In addition to automated analysis, blood smears were prepared and stained with Diff-Quik for cytological evaluation. Smears were examined microscopically to confirm platelet morphology and identify megathrombocytes (indicated by blue arrows) and platelets of normal size (indicated by black arrows), as illustrated in Fig. 1.

2.7. Statistical analysis

Statistical analyses were performed to evaluate the diagnostic and prognostic relevance of PLCC and PLCR in cats with HCM. Analyses were conducted using SigmaPlot Statistical and Graphing Software (California, USA) and MedCalc (version 20.218, Ostend, Belgium).

Descriptive statistics were used to summarize hematologic parameters. PLCC and PLCR values were initially compared across three major clinical subgroups: healthy controls (Stage A), cats with asymptomatic HCM (Stages B1 and B2), and cats with symptomatic HCM (Stages C and D). Additional subgroup analyses were performed according to the five-stage classification of HCM defined by the ACVIM consensus guidelines (Luis Fuentes et al., 2020). Furthermore, comparisons were made between HCM cats with and without confirmed FATE, and between those diagnosed with HCM ($n = 32$) and HOCM ($n = 18$).

For group comparisons, one-way analysis of variance (ANOVA) was used when data met assumptions of normality and homogeneity of variance. The Kruskal–Wallis H test (non-parametric one-way ANOVA) was applied when these assumptions were violated. Post hoc analyses were conducted using the Holm–Sidak method for multiple pairwise comparisons against the control group. Results were visualized using box plots, with medians and interquartile ranges (25th and 75th percentiles) displayed.

Associations between PLCC or PLCR and other hematologic parameters, including platelet indices and differential white blood cell (WBC) counts, were assessed using Pearson correlation analysis.

To determine the diagnostic performance of PLCC and PLCR in predicting thromboembolic risk, an area under the receiver operating characteristic curve (AUC-ROC) analysis was performed. The optimal cut-off values for thromboembolism prediction were identified along with corresponding sensitivity, specificity, AUC, standard deviation (SD), and positive (+LR) and negative (−LR) likelihood ratios.

Machine Learning–Based Predictive Modeling: In addition to conventional statistical methods, a supervised machine learning approach was used to determine whether hematological parameters, along with sex and age, could predict the risk of FATE. A binary classification model was developed using the Extreme Gradient Boosting (XGBoost) algorithm, which efficiently handles non-linear feature interactions and variable importance ranking in biomedical datasets. The model was trained to distinguish between FATE-positive (1) and non-FATE (0) cats, including HCM subgroups B1—D. Healthy controls were excluded to focus exclusively on pathological disease progression. Model optimization was performed via cross-validation.

Model Explainability – SHAP Analysis: To interpret model outputs, SHapley Additive exPlanations (SHAP) analysis was performed. SHAP values quantify the impact of each variable on individual predictions, providing a transparent view of model behavior. Unless otherwise specified, all descriptive data are presented as mean ± standard deviation (SD). A P-value <0.05 was considered statistically significant.

3. Results

The clinical characteristics of the study population are summarized in Table 1. British Shorthair, British Longhair, and Scottish Fold were the breeds most represented. No significant differences in mean age or body weight were observed between groups. As expected, IVS and LVPW thicknesses and LA diameters were significantly greater in cats with more advanced HCM stages than healthy controls (Stage A), consistent with ACVIM classification criteria (Fig. 2). WBC counts were recorded but were used solely for correlation analyses.

Analysis of platelet indices revealed that PLCR increased progressively with disease severity. In healthy controls, mean PLCR was 68.8 ± 6.2 %, compared to 75.7 ± 4.9 % in symptomatic HCM cats (Stages C and D), a statistically significant difference ($P < 0.01$; Fig. 3). PLCC and MPV were also significantly elevated in asymptomatic and symptomatic HCM groups compared to healthy controls ($P < 0.01$ and $P < 0.05$, respectively).

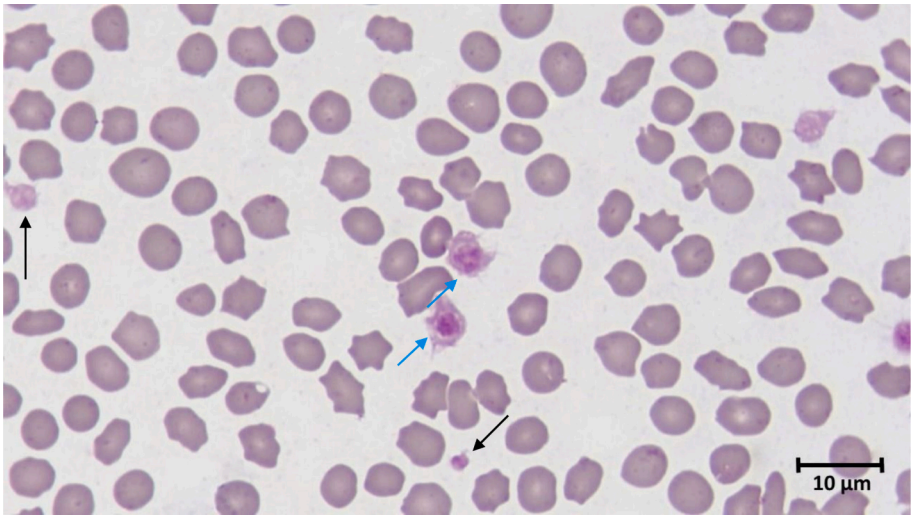

Fig. 1. Blood smears stained with Diff-Quik. Smears were examined microscopically (x100) to evaluate platelet morphology and identify megathrombocytes (blue arrows) and platelets of normal size (black arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

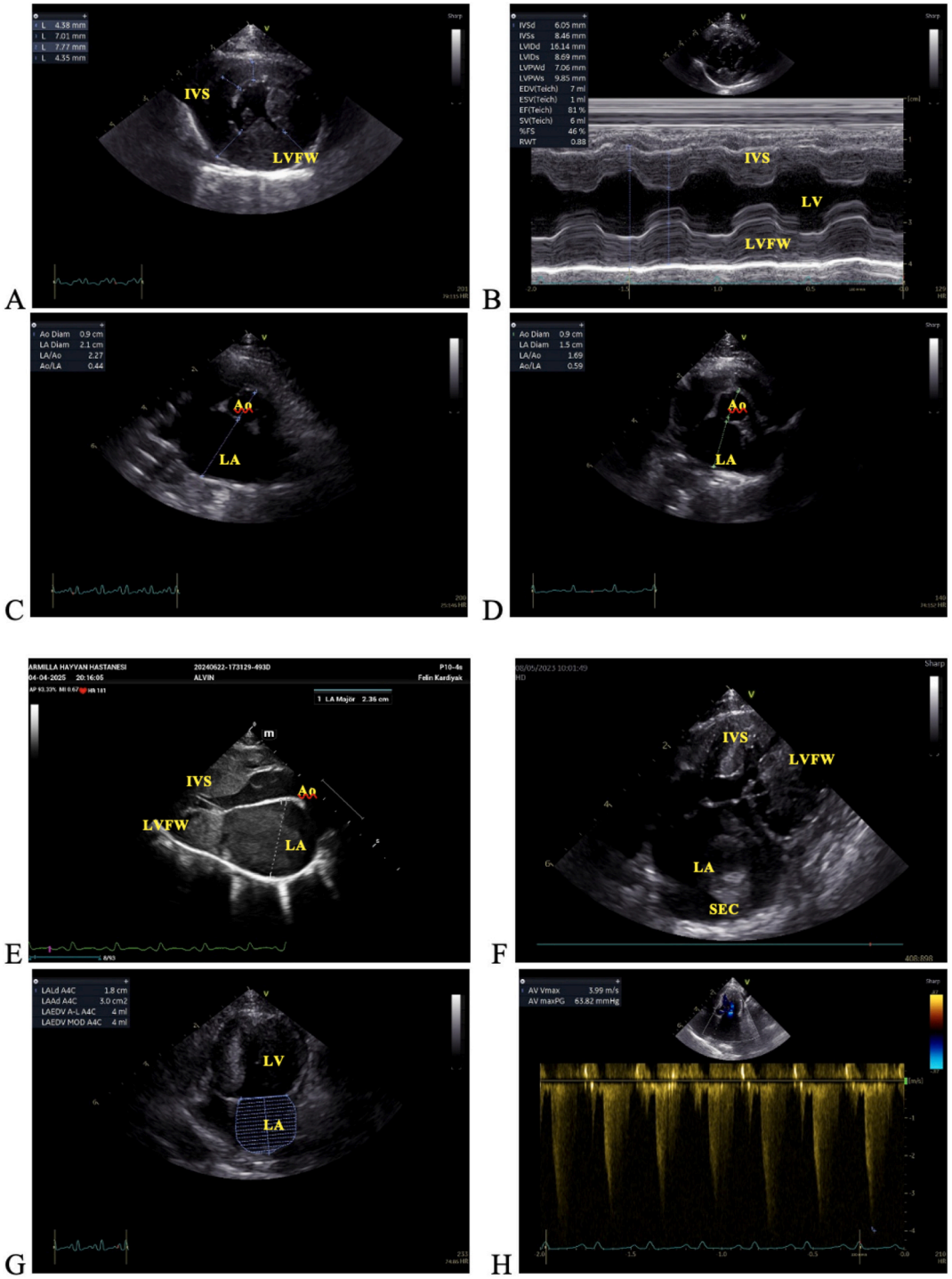

Fig. 2. Echocardiographic images obtained from cats with varying severity of hypertrophic cardiomyopathy in this study. The interventricular septum (IVS) and/or left ventricular posterior wall (LVPW) thickness from papillary muscles levels are shown in the right parasternal short axis view (RPSAx) using two-dimensional (A) and M-mode echocardiography (B). An echocardiographic image of a cat with HCM demonstrated the thickening of both the interventricular septum and the left ventricular free wall, while the left atrial dimension increases (C) or remains within normal limits (D). Increased left atrial (LA) volume and size with spontaneous echo contrast (SEC) are demonstrated in the right parasternal long axis view (RPLAx) (E). The left apical four-chamber view reveals left atrial dilation (F), volume overload (G), and thrombus formation within the left atrium (F). Increased aortic (Ao) velocity suggests the presence of hypertrophic obstructive cardiomyopathy. The shape of the aortic flow is consistent with dynamic left ventricular outflow tract obstruction (DLVOTO) (H).

When comparing individual ACVIM stages (B1 through D), PLCR demonstrated a non-significant upward trend: 66.3 ± 8.8 % in Stage B1, 68.0 ± 9.7 % in Stage B2, 71.4 ± 8.3 % in Stage C, and 75.3 ± 6.8 % in Stage D (Fig. 4). Although the trend was apparent, inter-stage differences did not reach statistical significance. PLCC followed a similar non-linear pattern, with values of 136 ± 72 in B1, 155 ± 46 in B2, and a marked increase in Stage C (188 ± 97), followed by a decline in Stage D (119 ± 63). Due to high variability, these differences were not statistically significant. PDW was the only parameter that differed significantly among HCM stages.

In comparisons involving thromboembolic complications, cats with confirmed FATE had significantly lower PLCC values (71 ± 35 × 10^9/L)

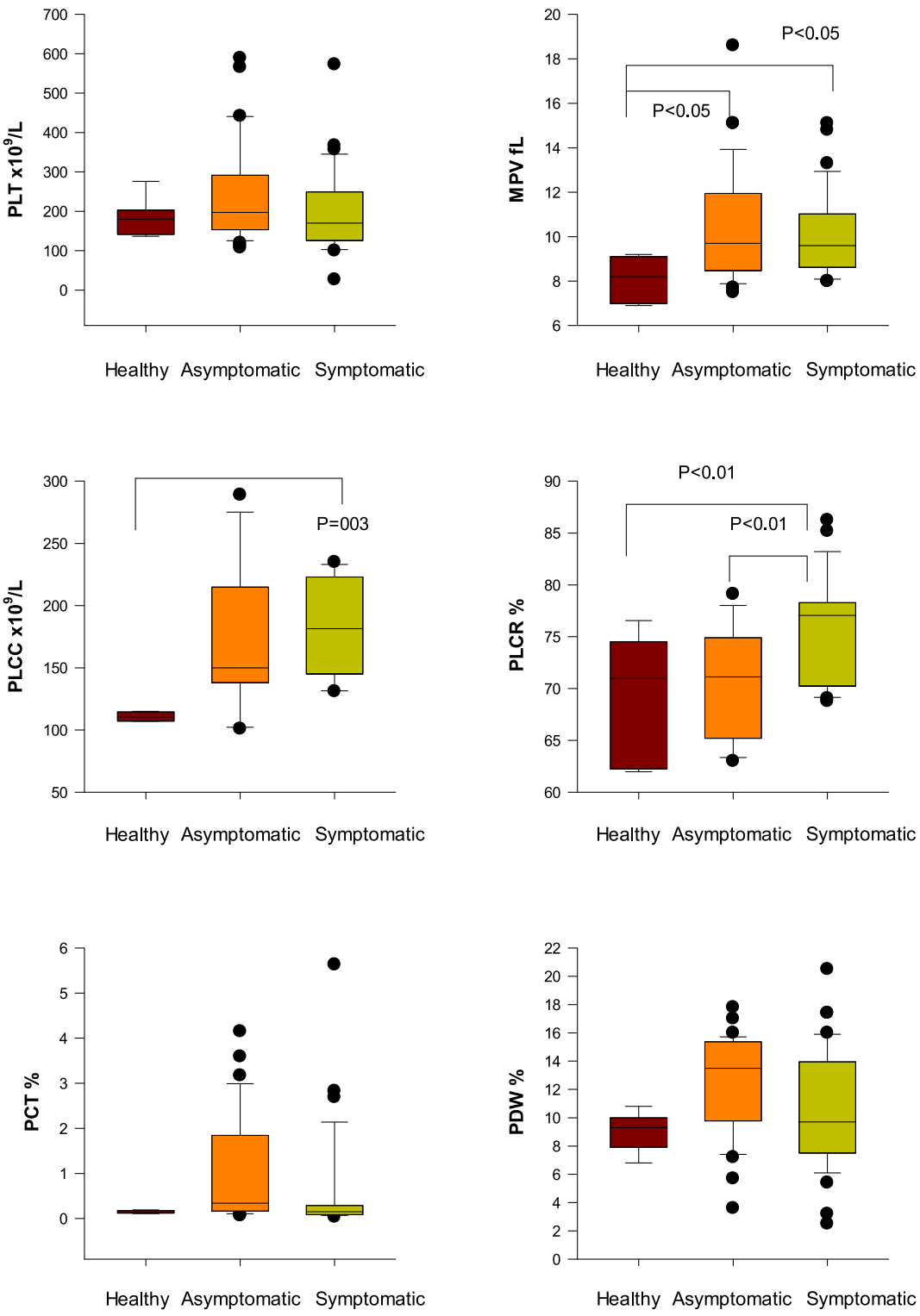

Fig. 3. Platelet indices in cats with different stages of hypertrophic cardiomyopathy (HCM), classified according to the ACVIM consensus statement (Luis Fuentes et al., 2020). 'Healthy' corresponds to Stage A (control group), 'asymptomatic' includes Stages B1 and B2 without clinical signs, and 'symptomatic' includes Stages C and D with clinical signs of HCM. The box plot shows median, 25th, and 75th percentiles. PLT: Platelet, MPV: Mean platelet volume, PLCC: Platelet large cell count, PLCR: Platelet large cell ratio, PCT: Plateletcrit, and PDW: Platelet distribution width.

than both healthy controls (123 ± 26 × 10^9/L) and HCM cats without FATE (133 ± 63 × 10^9/L; $P < 0.05$; Fig. 5). MPV was also significantly elevated in the FATE group (10.6 ± 2.3 fL) compared to controls (8.1 ± 0.9 fL; P < 0.05). Although PLCR was mildly increased in the FATE group, the difference was not statistically significant.

No statistically significant difference in platelet indices was found between cases with HCM and HOCM and healthy controls (data not shown).

Correlation analyses (Table 2) revealed a significant negative relationship between platelet count and PLCR (P < 0.05) and a strong positive correlation between platelet count and PLCC ($P < 0.001$). PLCC also correlated positively with PDW and total white blood cell count (P

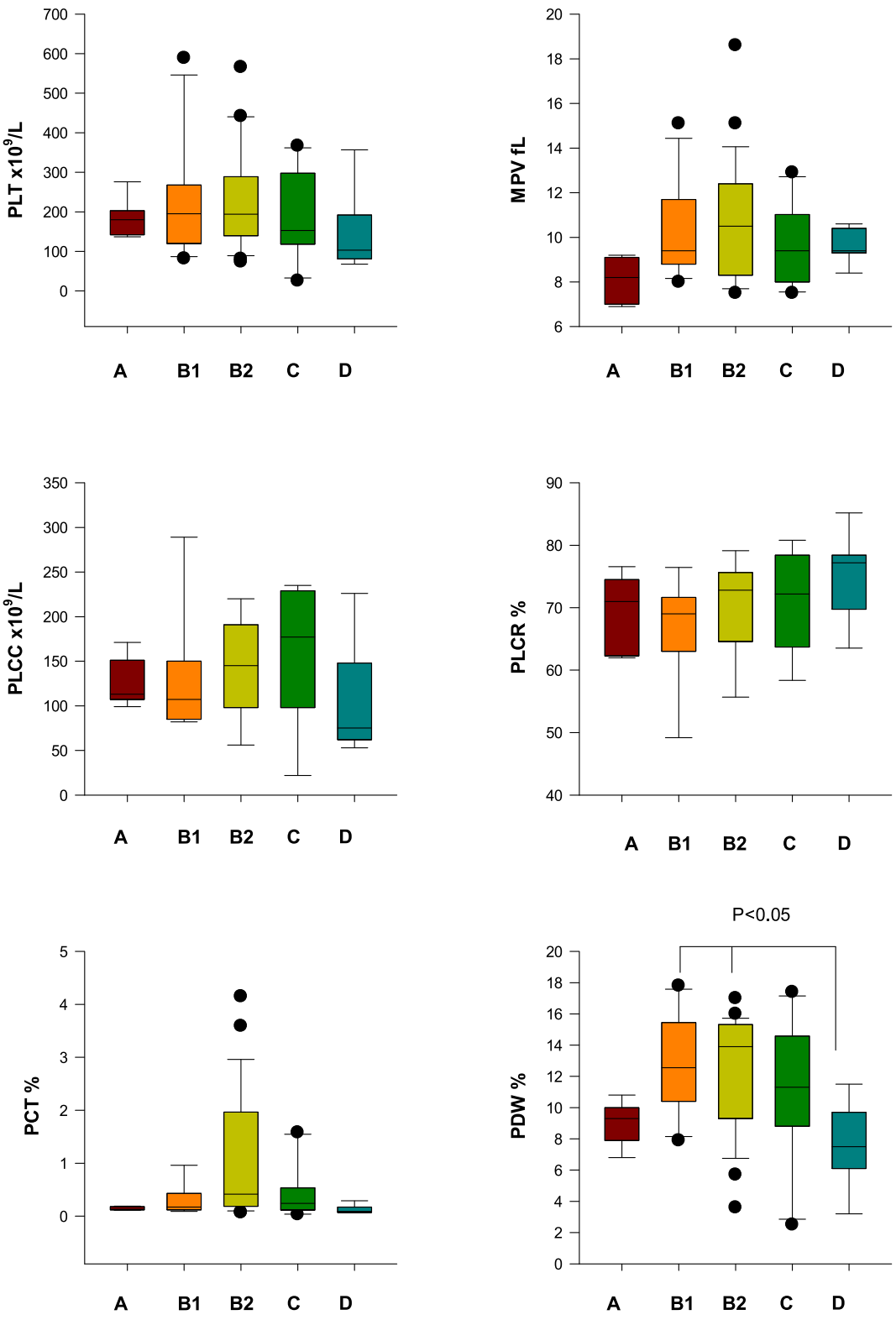

Fig. 4. Platelet indices in cats with the different stages of hypertrophic cardiomyopathy (HCM) diagnosed according to the ACVIM consensus statements (Luis Fuentes et al., 2020). Abbreviations and group definitions are already detailed in Fig. 3.

< 0.05), suggesting a potential association between platelet activation and systemic inflammatory markers.

ROC curve analysis was used to evaluate the discriminatory ability of PLCC and PLCR in predicting thromboembolic risk (Table 3). PLCC demonstrated the highest diagnostic performance, with an area under the curve (AUC) of 0.835. A cut-off value of $\leq 74 \times 10^9$/L yielded a sensitivity of 71 % and a specificity of 84 %. In contrast, PLCR had a lower AUC (0.561); although a cut-off value of >69 % provided high sensitivity (85 %), the associated specificity (40 %) and likelihood ratios suggested limited clinical utility.

The XGBoost classifier, applied to the data selected for this analysis, achieved an ROC-AUC analysis of 0.68, as shown in Fig. 6. Feature-

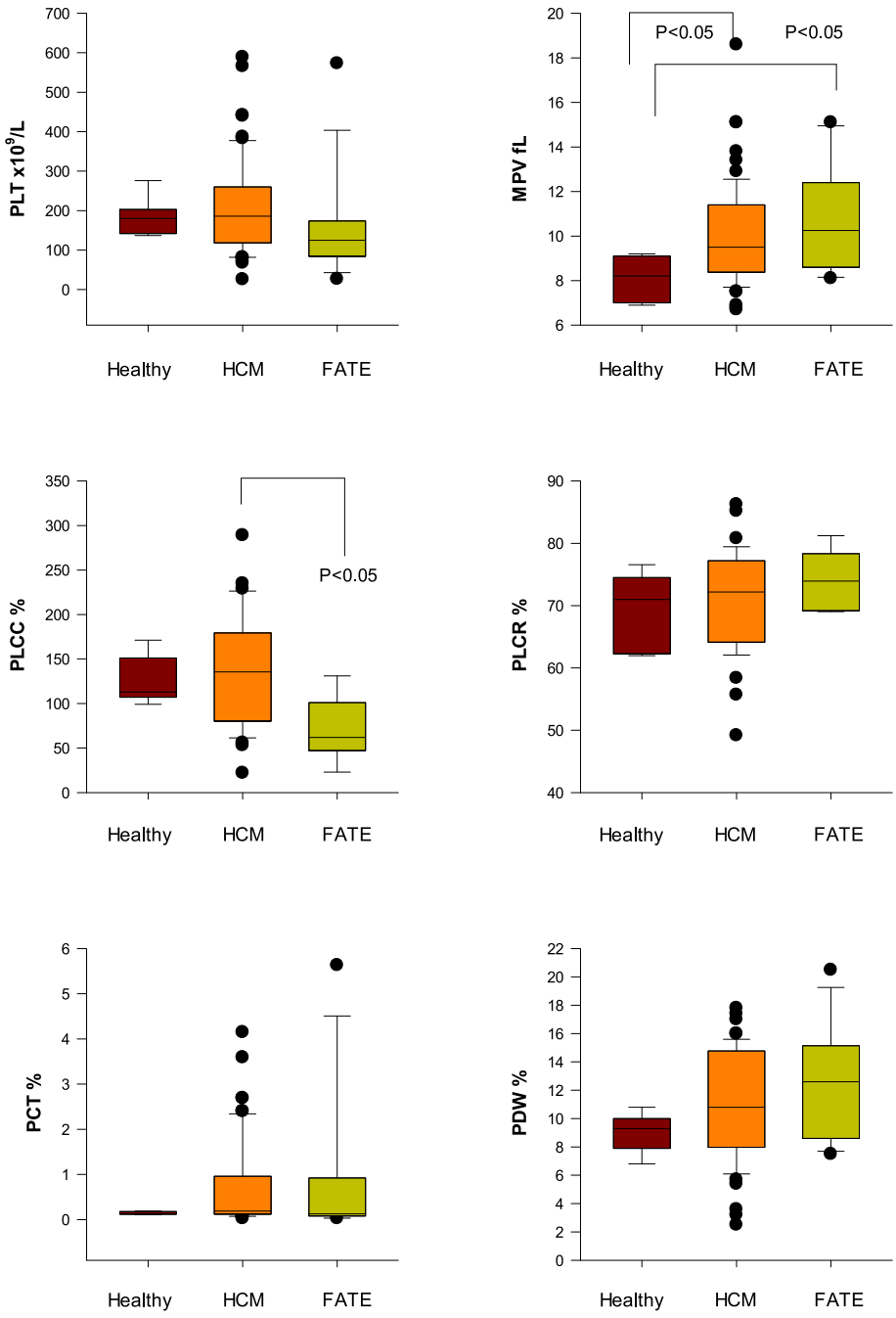

Fig. 5. Platelet indices in cats with hypertrophic cardiomyopathy (HCM) complicated with or without arterial thromboembolism (FATE). Abbreviations and group definitions are provided in Fig. 3.

specific SHAP dependence plots (Fig. 7) were generated to visualize the non-linear relationships between the most impactful variables and model predictions.

4. Discussion

This study offers new insights into the diagnostic and prognostic value of PLCC and PLCR in fHCM. While conventional platelet metrics such as platelet count, MPV, and PCT demonstrated limited discriminatory capacity, PLCC and PLCR displayed distinct patterns associated with disease presence, clinical stage, and thromboembolic complications. These findings highlight the potential of these advanced indices as accessible and clinically relevant biomarkers for evaluating fHCM.

PLCC was significantly elevated in cats with HCM compared with healthy controls, and this elevation was evident even in asymptomatic stages. This finding suggests that an increased presence of large platelets may precede the onset of clinical signs and reflect early platelet activation in response to myocardial remodeling. Large platelets are metabolically and enzymatically more active and are considered to possess greater thrombotic potential. These results align with findings from both human and veterinary studies, where increased PLCC has been associated with cardiovascular and inflammatory states (Çolakoğlu et al., 2018; Handtke and Thiele, 2020; Khandekar et al., 2006; Koupenova et al., 2016; Yilmaz et al., 2008).

Paradoxically, PLCC was significantly reduced in cats with HCM complicated by FATE despite elevated MPV in this group. This apparent discrepancy may be explained by platelet consumption at sites of thrombus formation, a hallmark of hypercoagulable states. Large,

Table 2
Pearson correlations between PLCR and PLCC, and other platelet indices.

	PLCR	PLCC
PLCC	*r*:-0.114 $P = 0.556$	*
PLT	*r*:-0.323 $P = 0.027$	*r*:0.700 $\mathbf{P = 0.001}$
MPV	*r*: 0.151 $P = 0.311$	*r*: 0.270 $P = 0.156$
PDW	*r*:-0.021 $P = 0.888$	*r*: 0.402 $\mathbf{P = 0.030}$
PCT	*r*: 0.084 $P = 0.572$	*r*: 0.267 $P = 0.169$
WBC	*r*:0.018 $P = 0.903$	*r*:0.361 $\mathbf{P = 0.05}$
Neutrophil	*r*:-0.323 P = 0.027	*r*: 0.311 $P = 0.100$
Lymphocyte	*r*:-0.181 $P = 0.229$	*r*:-0.209 $P = 0.277$

Abbreviations were provided in the Fig. 2 legend. Bold values show a statistically significant interaction between variables.

metabolically active platelets are preferentially recruited to thrombi, and their sequestration may lead to a transient depletion of circulating PLCC. This pattern is consistent with prior observations in fHCM (Çolakoğlu et al., 2018; Kocatürk et al., 2023a) and mirrors findings in human patients with acute thrombotic events, where activated platelets are rapidly incorporated into evolving thrombi, resulting in lower peripheral counts of large platelets (Mathur et al., 2001; Wada et al., 2018).

PLCR, although not significantly different in all pairwise comparisons, exhibited a progressive increase across HCM stages, reaching peak values in symptomatic cats (Stage C/D). This trend suggests that the proportion of large, potentially hyperactive platelets rises in parallel with disease severity, potentially reflecting sustained or repeated platelet activation as myocardial pathology advances. In human medicine, elevated PLCR has been associated with increased platelet reactivity, vascular injury, and worse outcomes in patients with coronary artery disease, stroke (Kannappalli et al., 2025; Khandekar et al., 2006), and pulmonary thromboembolism (Akgün et al., 2023). Notably, PLCR levels have been shown to correlate with thrombus diameter, supporting its link to thrombotic burden (Akgün et al., 2023). While the diagnostic value of PLCR in feline cardiology remains unexplored mainly, our findings suggest that it may serve as a dynamic marker of platelet stress and cardiovascular disease progression in cats.

The strong positive correlation between PLCC and both PLT count and PDW supports the interpretation that PLCC reflects the size, heterogeneity, and functional activity of circulating PLTs. This reinforces its potential value as an integrative marker of PLT dynamics in fHCM. Conversely, the inverse correlation between PLCR and neutrophil count may suggest an interaction between systemic inflammation and PLT activation. This relationship is clinically relevant, as prior studies have associated leukocytosis with poorer outcomes in cats with cardiac disease (Fries et al., 2022; Gavazza et al., 2021), indicating that inflammatory status may modulate PLT behavior and contribute to disease progression (Yuri Gasparyan et al., 2011).

Among all evaluated PLT indices, PLCC demonstrated the strongest diagnostic performance for predicting thromboembolic risk in cats with HCM, with the ROC-AUC analysis of 0.835 and an optimal cut-off value of $\leq 74 \times 10^9$/L. This finding supports its potential utility as a clinically informative biomarker for identifying cats at elevated risk of ATE, possibly reflecting increased PLT activation or turnover, as previously reported in human cardiovascular disease (Garcia-Pachon et al., 2020). In contrast, while PLCR exhibited high sensitivity, its limited specificity diminishes its diagnostic value as a standalone test in this setting. Similarly, conventional indices such as MPV, PDW, and PCT failed to discriminate between cats with and without thromboembolic complications. This suggests these parameters lack sufficient sensitivity to detect clinically relevant PLT activation in fHCM. Nonetheless, it is worth noting that elevated PDW has been associated with valvular thrombosis in humans with mechanical valve prostheses (Pourbashash et al., 2025), and its relevance to feline thromboembolism remains to be fully elucidated.

The XGBoost model achieved moderate but biologically meaningful discriminative performance (ROC-AUC = 0.68), indicating that hematologic data harbor a detectable prothrombotic signal associated with FATE. SHAP analysis highlighted PLT indices, particularly PLCC and PLCR%, as key contributors to risk prediction. Higher PLCC values were consistently associated with increased FATE probability, particularly when hematocrit (HCT) levels were elevated. This suggests that thromboembolic risk may arise from the combined effects of PLT activation and erythrocyte-related hemodynamic factors. In contrast, PLCR % showed a context-dependent contribution to risk, with the greatest influence observed when accompanied by elevated neutrophil counts or high MPV and PLT values, highlighting the interplay between PLT reactivity and systemic inflammation. Collectively, these results indicate that PLCC serves as a robust hematologic marker of thromboembolic potential, while PLCR% reflects inflammation-modulated PLT activity contributing synergistically to FATE development in cats with HCM.

Stage D HCM cats were receiving cardiac medications at the time of blood sampling, which may have influenced their hematologic and PLT-derived indices. High-dose furosemide can inhibit ADP-induced platelet aggregation and, in rare cases, contribute to immune-mediated thrombocytopenia (Chandok et al., 2022). ACE inhibitors, such as enalapril, may reduce PLT activation and exert antithrombotic and endothelium-protective effects (Ekholm et al., 2024), while pimobendan shows concentration-dependent antiplatelet effects in vitro but no measurable inhibition at therapeutic oral doses in cats (Kennerly et al., 2023). Beta-blockers such as atenolol can reduce PLT adhesion, though their effect on aggregation is limited (Bonten et al., 2014). In addition, Stage D cats at high risk of ATE received clopidogrel combined with factor Xa inhibitors (rivaroxaban or apixaban) to exploit a synergistic mechanism that concurrently inhibits $P2Y_{12}$-mediated PLT activation and factor Xa–dependent thrombin generation, enhancing thromboembolic protection (Hogan et al., 2004; Lo et al., 2023). Collectively, these observations indicate that hematologic and PLT-derived indices in Stage D cats likely reflect both underlying disease and pharmacologic modulation. Accordingly, caution is warranted when comparing these results to earlier HCM stages, although the observed trends remain informative

Table 3
Optimum cut-off values of platelet indices for thromboembolic risk prediction in cats with hypertrophic cardiomyopathy, with corresponding sensitivity, specificity, area under the curve (AUC), standard error (SD), and positive (+LR) and negative (−LR) likelihood ratios.

Parameter	Cut-off	Sensitivity (%)	Specificity (%)	AUC	SE	+LR	-LR
PLCC x10^9/L	≤74	71.43	84.62	0.835	0.0825	4.64	0.34
PLCR %	>69.03	85.71	40.74	0.561	0.134	0.96	1.05
PLT x10^9/L	≤126	57.14	73.53	0.668	0.0898	2.16	0.58
MPV fL	>10.6	50.00	82.86	0.652	0.0920	2.92	0.60
PCT %	≤0.13	61.54	57.14	0.567	0.107	1.44	0.67
PDW %	>12.2	50.00	78.79	0.622	0.098	2.36	0.63

PLCC: Platelet large cell count, PLCR: Platelet large cell ratio, PLT: Platelet, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width.

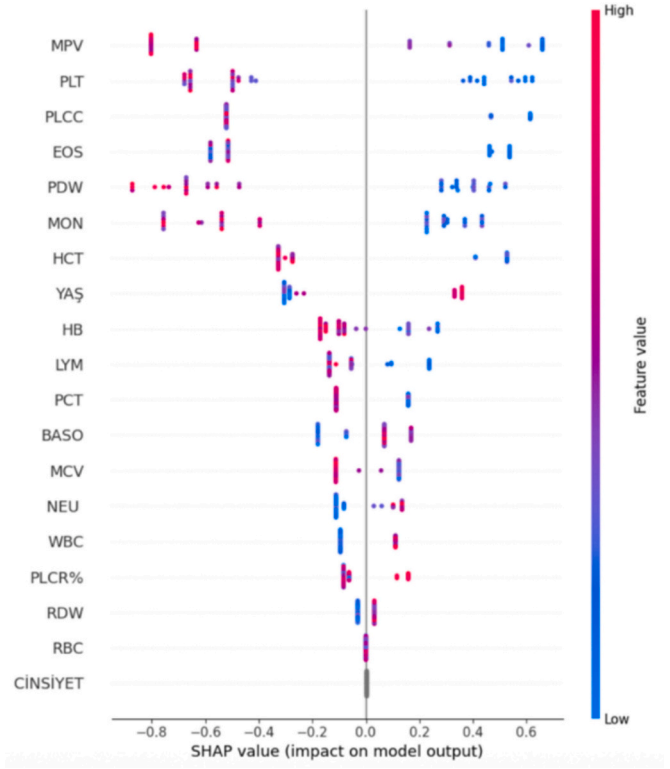

Fig. 6. SHAP summary plot illustrating the relative impact of hematological variables on FATE prediction using the XGBoost model (n = 71). Platelet-related markers, including PLCC, PLCR%, MPV, and PLT, were the strongest contributors to positive risk prediction. In contrast, erythrocyte indices such as HCT and RBC were predominantly associated with lower FATE probability. Each point represents an individual case, with color indicating the underlying feature value.
Abbreviations: MPV, mean platelet volume; PLT, platelet; PLCC, platelet large cell count; EOS, eosinophil; PDW, platelet distribution width; MON, monocyte; HCT, hematocrit; AGE, years; HB, hemoglobin; LYM, lymphocyte; PCT, plateletcrit; BASO, basophil; MCV, mean corpuscular volume; NEU, neutrophil; WBC, white blood cell count; PLCR%, platelet large cell ratio; RDW, red blood cell distribution width; RBC, red blood cell count

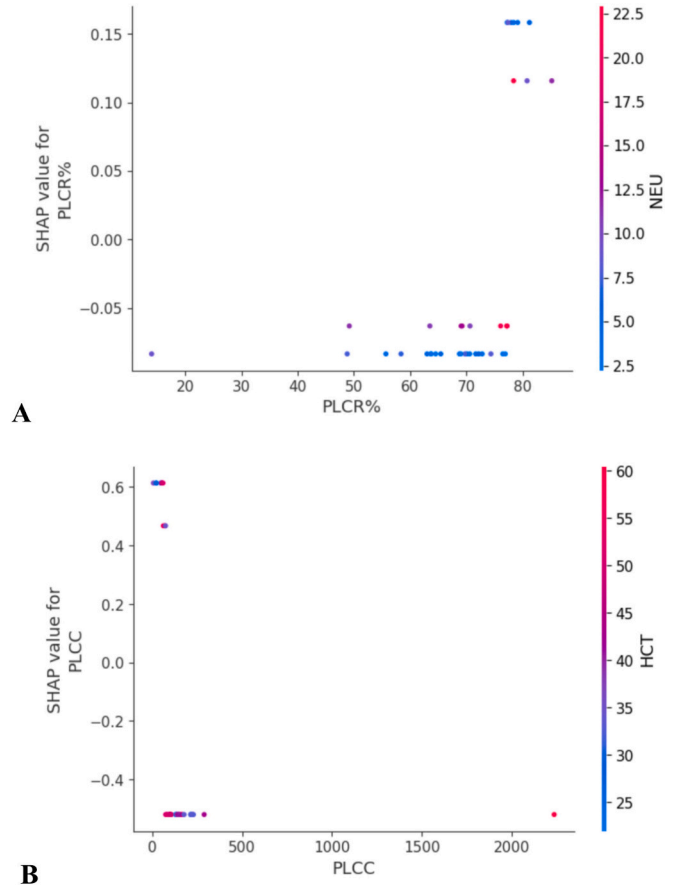

Fig. 7. SHAP Dependence Plot Showing Interaction Between platelet parameters (PLCR% and PLCC) and Neutrophil Count (NEU) and Hematocrit (HCT) in Predicting FATE Risk. (A) The effect of PLCR% varies with NEU levels, and (B) higher PLCC values, influenced by HCT levels, are associated with increased SHAP scores and higher predicted FATE risk.

for assessing thrombotic risk in advanced disease.

This study has several limitations that should be acknowledged when interpreting the findings. First, the small sample size, particularly in the FATE group, may have limited the statistical power to detect subtle yet clinically meaningful differences in PLT indices. Previous studies investigating hematologic and hemostatic markers in feline cardiology have reported comparable constraints in statistical robustness due to limited cohort sizes (Fuentes, 2012). Second, the cross-sectional design precluded the assessment of temporal changes in PLT indices. Longitudinal monitoring of PLCC and PLCR may provide more accurate insight into their prognostic value and the dynamics of thrombotic risk, as suggested by analogous trends in human cardiology (Chu et al., 2010). Third, although efforts were made to minimize confounding, factors such as systemic inflammation and concurrent comorbidities could not be entirely excluded. Inflammatory responses are known to influence platelet size, heterogeneity, and reactivity across species, including cats (Donato et al., 2023), dogs (Yilmaz et al., 2008), and humans (Yuri Gasparyan et al., 2011), and may have contributed to the observed variability in PLCC and PLCR. Finally, this study did not incorporate functional assays of PLT activation, such as thromboelastography, aggregometry, or flow cytometry, which limits the mechanistic interpretation of the observed changes (Cremer et al., 2018; Johnson et al., 2024; Kocatürk et al., 2023a; Tablin et al., 2014). Future investigations integrating such methodologies are needed to validate PLCC and PLCR as biomarkers of PLT activity and thromboembolic risk in fHCM. In addition, the VH5R analyzer used for CBC analysis in the study determines PLT counts using the impedance (Coulter principle) method, a technique also employed by several commonly used veterinary hematology analyzers that utilize impedance in combination with laminar or laser flow cytometry. Therefore, the PLT indices obtained in this study are considered broadly comparable and clinically applicable to other impedance-based systems. Minor variations may occur when comparing results generated from optical or flow cytometry-based instruments, and these differences should be systematically evaluated in future studies.

5. Conclusion

This study highlights the potential clinical relevance of PLCC and PLCR as supportive markers in assessing cats with HCM. An elevated PLCC in asymptomatic stages may indicate early platelet activation, while a reduced PLCC in cats with thromboembolic complications likely reflects platelet consumption secondary to thrombus formation. A progressive rise in PLCR with advancing disease stages may further indicate ongoing platelet turnover or activation. These indices may assist clinicians in identifying cats at increased thrombotic risk and support decisions regarding closer monitoring or prophylactic treatment. Prospective studies with longitudinal follow-up are needed to clarify their role in everyday clinical practice and to evaluate their effectiveness in tailoring antithrombotic therapy in feline cardiology.

CRediT authorship contribution statement

Didem Algan: Writing – original draft, Data curation. **Tuğba Varlik:** Data curation. **Jørgen Koch:** Supervision. **Zeki Yilmaz:** Writing – review & editing, Writing – original draft, Supervision, Investigation.

Informed consent statement

Written informed consent was not obtained from the dog owners before their dogs participated in the study, because this was a retrospective study in which data were collected from the animal hospital archives.

Institutional review board statement

The materials of this study were collected retrospectively from the patient archive at the Animal Teaching Hospital for Companion Animals (Bursa Uludag University, Veterinary Faculty, Bursa, Türkiye) and the private pet hospitals.

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There is no foundation for this research, including routine diagnostic work-up in the Animal Teaching Hospital(Bursa Uludag University, the Faculty of Veterinary Medicine, Bursa, Turkey) and the private pet hospitals.

Declaration of competing interest

The authors declare that they have no competing interests to disclose. There are no financial, personal, or professional relationships that could be construed as having influenced the design, conduct, analysis, or reporting of this research. No part of this study was influenced by any commercial or financial support, and the authors have no affiliations with organizations that could be perceived to have a vested interest in the outcomes of this work.

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Data availability

Data were available in the archive of the Veterinary Teaching Hospital and the private clinics.

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