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Causes of thrombocytopenia in dogs in the United Kingdom: A retrospective study of 762 cases

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Abstract

Background: Thrombocytopenia is a common laboratory abnormality in dogs, and numerous diseases have been associated with its development. Estimates for the sensitivity and specificity of the degree of reduction of platelet concentration for the diagnosis of primary immune-mediated thrombocytopenia (pITP) have not been reported.

Objectives: To report the prevalence of different causes of thrombocytopenia in dogs in the United Kingdom and to investigate the utility of platelet concentration to differentiate causes of thrombocytopenia.

Methods: Medical records of 762 dogs with thrombocytopenia presented to seven referral hospitals from January 2017 to December 2018 were retrospectively reviewed. Cases were assigned into the following categories: pITP, infectious diseases, neoplasia, inflammatory/other immune-mediated disorders and miscellaneous causes. The prevalence of the different categories was estimated, and platelet concentrations were compared. Receiver-operating characteristic (ROC) curves were used to investigate the utility of platelet concentration to differentiate between causes of thrombocytopenia.

Results: The most common disease category associated with thrombocytopenia was neoplasia (27.3%), followed by miscellaneous causes (26.9%), pITP (18.8%), inflammatory/immune-mediated disorders (14.4%) and infectious diseases (12.6%). Dogs with pITP had significantly lower platelet concentrations (median 8×10^9/L, range: 0–70×10^9/L) than dogs in the other four categories. Platelet concentration was useful for distinguishing pITP from other causes of thrombocytopenia (area under ROC curve = 0.89, 95% confidence interval 0.87, 0.92), with a platelet concentration $\leq 12 \times 10^9$/L being 60% sensitive and 90% specific.

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Conclusions: Severe thrombocytopenia was highly specific for a diagnosis of pITP, which was more prevalent in this UK population of thrombocytopenic dogs compared with previous epidemiological studies. Conversely, the proportion of dogs with infectious diseases was lower than in previous reports from other locations.

KEYWORDS
canine, platelets, prevalence, thrombocytopenia, United Kingdom

1 | INTRODUCTION

Thrombocytopenia is a common laboratory abnormality in dogs, with a reported prevalence of 5.1%–6.7% in previous studies undertaken in North America and Germany (Botsch et al., 2009; Grindem et al., 1991). Thrombocytopenia can develop due to numerous different processes: decreased production, increased consumption/loss, sequestration and destruction (Brooks, 2017; Feldman et al., 1988, Neel et al., 2014). More than one pathophysiological mechanism can occur in the same disorder, further complicating diagnostic and therapeutic decisions.

Assessment of platelet concentration can be challenging, as automated counts can be inaccurate due to misidentification of cell types or platelet clumping (Koplitz et al., 2001). Manual platelet concentration determination on blood smear review is typically considered more reliable (Brooks, 2017; Lewis & Meyers, 1996; Neel et al., 2014), but clumping of platelets, if seen, precludes a precise estimation.

The prevalence of primary immune-mediated thrombocytopenia (pITP) was around 5% in two studies looking at causes of thrombocytopenia (Botsch et al., 2009; Grindem et al., 1991); however, the prevalence differed between the two studies for thrombocytopenia related to other aetiologies: 13% vs. 28% for neoplasia, 23% vs. 34.9% for infectious or inflammatory disease and 59% vs. 25.5% for miscellaneous or multifactorial causes. The most recent study assessing diseases associated with thrombocytopenia in mainland Europe was published a decade ago (Botsch et al., 2009) and, since that time, advanced diagnostics (particularly imaging modalities and clonality testing) have progressed, potentially altering the final diagnosis in some cases. Additionally, no studies have analysed the disease distribution of canine thrombocytopenic patients in the United Kingdom, where the prevalence of infectious causes may be expected to be lower than in studies conducted elsewhere (Folly et al., 2020; O'Neill et al., 2014).

Although thrombocytopenia can be defined as any platelet concentration below the reference range, the severity of the reduction is often deemed to be an important factor to assess the risk of bleeding. Spontaneous haemorrhage is seldom caused by thrombocytopenia at concentrations of $>30 \times 10^9$/L (Brooks, 2017; Cines & Blanchette, 2002; Williams & Maggio-Price, 1984). In a previous study, dogs with pITP and thrombocytopenia caused by disseminated intravascular coagulation (DIC) had significantly lower platelet concentrations (median 32.0×10^9 and 55.0×10^9/L, respectively) than dogs with other causes of thrombocytopenia (Botsch et al., 2009). Although numerous other studies have reported a significant difference in platelet concentration in dogs with pITP (Grindem et al., 1991; Lewis & Meyers, 1996; Neel et al., 2014; Putsche & Kohn, 2008), estimates for the sensitivity and specificity of the degree of reduction of platelet concentration for the diagnosis of pITP have not been reported.

The aim of the present study was two-fold. The first objective was to report the causes of thrombocytopenia in a cohort of dogs thoroughly assessed at different referral hospitals throughout the United Kingdom. We hypothesised that thrombocytopenia associated with vector-borne diseases would account for <1% within our UK population. The second objective was to determine the utility of platelet concentration in identifying the aetiology of thrombocytopenia in dogs.

2 | MATERIALS AND METHODS

2.1 | Study population and inclusion criteria

Eligible cases for this study were identified from a search of electronic medical records at seven referral hospitals located in different geographic areas of the United Kingdom. Dogs were presented to these centres from January 2017 to December 2018. Cases were included if the automated platelet concentration was below the reference limit given by the analyser used in each centre, provided that thrombocytopenia was confirmed by a manual estimated concentration upon blood smear examination. Any degree of platelet clumping or incomplete medical records were considered exclusion criteria. Dogs were also excluded when more than one condition was diagnosed if this precluded an accurate classification on one of the disease categories established.

On-site analysers were different between referral institutions: Siemens ADVIA 2120 Hematology System (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) at institutions 1, 2, 4 and 6, IDEXX ProCyte Dx Haematology Analyser (IDEXX Laboratories, Inc., Westbrook, ME, USA) at institutions 3 and 7, and Genesis Hematology Analysis System (Oxford Science Inc., CT, USA) at institution 5. Some of the samples from institution 5 were submitted to a reference laboratory (Veterinary Pathology Group, Synlab) and analysed with SYSMEX XT2000i (Sysmex Corp., Kobe, Japan). Laboratory technicians evaluated the blood smears for erythrocytes, white blood cells and

platelet morphology, as well as for the presence of platelet clumping. Board-certified clinical pathologists reviewed the blood smears in some of the cases as well as all bone marrow cytology and biopsy samples, where performed. If multiple haematology results were available, the results of the first haematology performed at the referral institution showing that thrombocytopenia was included for statistical analysis. In some cases, thrombocytopenia was first identified by the referring veterinarian, and this result was included where the results were validated on the same sample at an external reference laboratory.

For each dog, signalment, clinical signs upon presentation to the referring veterinarian, vaccination status, travel history and medications administered within 1 month prior to referral were recorded. The following data regarding diagnostic investigations, where available, were recorded for each dog: haematology parameters, serum biochemistry abnormalities, coagulation tests (including prothrombin time [PT], activated partial thromboplastin time [aPTT] and D-dimers), antiplatelet antibody (APA) testing, antinuclear antibody analysis, diagnostic imaging technique(s) performed, infectious disease testing, urinalysis, urine culture and bone marrow aspiration and/or biopsy results, as well as any further diagnostic tests carried out. Mean platelet volume (MPV) was not included in the haematology panels of all the institutions, so the determination of the presence of macroplatelets was based on a subjective blood smear evaluation. Cases were categorised according to the diagnosis determined by the attending clinician of each case followed by a thorough review by the first author.

All cases were assigned to one of the following disease categories:

- **pITP**: This category included cases without an identifiable trigger for thrombocytopenia following extensive investigations (including haematology and comprehensive biochemistry panel and diagnostic imaging of the thorax/abdomen, as a minimum). Exclusion of infectious disease was only required in those dogs with a history of travel outside the United Kingdom. It was also recorded whether there was a response to immunosuppressive therapy with normalisation of the platelet concentration in the follow-up period for each dog, as an additional way to support this diagnosis. Dogs that were diagnosed with pITP after diligent search of a primary cause and died or were euthanised during the first 7 days of hospitalisation despite the treatment were also included.
- **Neoplasia**: This category contained dogs newly diagnosed with neoplasia based on histology and/or cytology. In cases where thrombocytopenia was too severe to safely collect tissue and/or cell samples, and no other disease had been identified, a diagnosis based on imaging findings was permitted (e.g. presence of a mass).
- **Infectious**: This category included dogs with positive serology, molecular testing or culture for bacterial, rickettsial, parasitic, protozoal, viral or fungal infectious agents or their cytological/histological identification. Cases were also included here if there was a high index of suspicion for bacterial infection, with no other identifiable cause of thrombocytopenia, with complete and persisting resolution of thrombocytopenia after treatment with antibiotics, even if bacterial culture was negative.
- **Inflammatory/immune-mediated disease other than pITP**: This category contained dogs where the predominant clinical and/or clinicopathological sign(s) were related to sterile inflammation (e.g. chronic hepatitis, pancreatitis) or disorders of suspected immune-mediated aetiology, other than pITP, without a cause or trigger for the predominant clinical signs after thorough investigation. This included conditions, such as immune-mediated haemolytic anaemia, immune-mediated polyarthritis (IMPA), systemic lupus erythematosus (SLE) or immunosuppressant-responsive enteropathy.
- **Miscellaneous disorders**: This category included dogs with a definitive diagnosis that did not fall into any of the other categories, for example toxin ingestion, presumptive reaction to vaccination, trauma, active haemorrhage and DIC of unknown aetiology. Patients that had received cytotoxic agents for the treatment of neoplasia and became thrombocytopenic were also included within this category.

Dogs with suspected inherited or breed-related thrombocytopenia were categorised in one of the above-mentioned disease categories based on the primary disease diagnosed, but a sub-analysis of the platelet concentration of these dogs was also performed separately.

2.2 | Statistical analyses

Data were collated and stored into a Microsoft Excel (Office 365) spreadsheet and imported into statistical software Stata (IC v.13.0) and SPSS 28.0 for Windows for coding and statistical analyses. The prevalence of the different disease categories was estimated. Normality for continuous variables (dog age [years] and haematological values [automated platelet concentration, haematocrit, white blood cells, segmented neutrophils, band neutrophils, monocytes, lymphocytes, eosinophils and basophils]) was assessed using the Shapiro–Wilk test, alongside visual assessment of distribution histograms with overlaid kernel density plots. Data were described as medians (interquartile range [IQR], range) due to the non-normal distribution. Categorical variables were described as proportions (%).

The Kruskal–Wallis test, followed by a post hoc Dunn's test with a Sidák adjustment for multiple comparisons, was used to compare haematological values and dog age across disease category groups. The Chi-square test was used to assess the relationship between categorical variables (the presence of macrothrombocytes, signs of bleeding, prolonged PT, prolonged aPTT, sex and neuter status) and disease category groups, and the Fisher Exact test was used to assess the relationship between breed and referral centre. Statistical significance was defined by a p-value <0.05.

Receiver-operating characteristic (ROC) curves and corresponding 95% confidence intervals were used to investigate the performance of automated platelet concentration for diagnosis of pITP.

3 | RESULTS

3.1 | Animals – age, gender and breed distribution

A total of 785 unequivocally thrombocytopenic dogs (i.e. with no platelet clumping documented on examination of the blood smear) were initially identified by all the institutions. Of these, 23 were excluded because of incomplete or insufficient medical records to allocate them into one of the disease categories, or where the diagnosis of more than one condition precluded an accurate classification on a given disease category.

The signalment of the general population of dogs assessed in all the seven institutions involved, regardless of the aetiology of thrombocytopenia, is shown in Table 1. The median age of all cases included was 7 years (range: 2 months to 18 years and 6 months). Three hundred and eighty-four (50.4%) were male dogs, and 378 (49.6%) were female dogs. Breeds most affected by thrombocytopenia included Spaniel breeds (Cocker spaniel, English springer spaniel, Sprocker and Cavalier King Charles spaniel [CKCS] – 188/762 [24.7%]), retrievers (158/762, [20.7%]) and terrier dogs (86/762, [11.3%]). Breed differences across the seven referral centres located in diverse geographical areas in the United Kingdom were not identified (Fisher's Exact p-value = 0.183).

3.2 | Classification of dogs by disease category

Of the 762 dogs with thrombocytopenia, 143 (18.8%) were included in the pITP category. All but 13 (9%) of these dogs responded to the immunosuppressive therapy with normalisation of the platelet concentration during the follow-up period available for each patient (1 month to 2.5 years). Thirteen dogs died or were euthanised during the first 7 days of hospitalization due to progressive deterioration of the disease; fatal internal haemorrhages and development of transfusion reactions were reported in 6/13 and 2/13 dogs, respectively. Regarding the remainder of the categories, 208 (27.3%) dogs were allocated in the neoplasia category, 96 (12.6%) in the infectious diseases category, 110 (14.4%) in the inflammatory/immune-mediated disorders (other than pITP) category and 205 (26.9%) in the miscellaneous diseases category. Table 2 shows disease subcategories and specific diagnoses given to the dogs by the primary clinician.

A significant relationship between disease group and sex (χ^2 16.7, p = 0.002) was identified, with the pITP group having the highest proportion of female dogs (95/148 [64.2%]). There also was a significant relationship between disease group and dog age (p = 0.0001), with post hoc analysis demonstrating that dogs with pITP were significantly younger (median 7.0 years, IQR 4.0, 9.0) than dogs with neoplasia (median 8.1 years, IQR 6.0, 10.0; p = 0.006) and older than dogs with infectious diseases (median 5.8 years, IQR 2.0, 8.0; p = 0.042). Conversely, there was no significant difference compared with inflammatory/immune-mediated (median 6.3 years, IQR 3.0, 8.8; p = 0.384) or miscellaneous disorders (median 6.0 years, IQR 2.8, 8.3; p = 0.073).

In 1.7% (13/762) of dogs in our population a vector-borne disease was identified, but only 26.4% (202/762) of dogs had any form of testing for these diseases. The point-of-care IDEXX SNAP 4Dx Plus test (IDEXX Laboratory, Westbrook, ME, USA) was performed in 24.5% (187/762) dogs for the screening of *Anaplasma phagocytophilum*, *Anaplasma platys*, *Borrelia burgdorferi*, *Ehrlichia canis*, *Ehrlichia ewingii* and *Dirofilaria immitis*, of which 4.8% (9/187) dogs tested positive. Eight out of nine dogs were positive for *Ehrlichia* spp. on IDEXX SNAP 4Dx Plus test, of which one was also positive to *Anaplasma* spp. One dog tested positive for *B. burgdorferi*. A diagnosis of ehrlichiosis was confirmed by polymerase chain reaction and immunofluorescence assay in four and two of the dogs, respectively, with no additional confirmatory tests performed in dogs diagnosed with *Anaplasma* spp. or *B. burgdorferi*. Of the nine dogs positive for at least one of the infectious agents tested in the IDEXX SNAP 4Dx Plus, seven were reported to have a history of travel (Southern Europe [5/7], Central America [1/7] or South-eastern Asia [1/7]), and in the remaining two, the travel history was unknown. Six dogs were diagnosed with leishmaniasis, two of which were also positive for *Ehrlichia* spp., and all six had travelled outside the United Kingdom.

Inherited or breed-associated thrombocytopenia was suspected by the primary clinician in 30 dogs. The main breed included in this subcategory was CKCS (n = 24), followed by sighthound breeds (n = 5) and Norfolk Terrier (n = 1), and macrothrombocytopenia was documented in all CKCS. In all these dogs, the thrombocytopenia was not associated with signs of bleeding, and the attending clinician assumed that this was an incidental finding when performing investigations for the presenting clinical signs. However, the DNA assay to determine the presence or absence of the β1-tubulin mutation was only performed in one of the dogs and was negative. Therefore, based on the diagnostic investigations, these dogs were included in the following groups: miscellaneous diseases (n = 16), neoplasia (n = 7), inflammatory/immune-mediated conditions other than pITP (n = 4) and infectious disorders (n = 3). Median-automated platelet concentration of the 30 dogs with suspected breed-related thrombocytopenia was 75 × 10^9/L (range: 14–184), and no statistical difference in the platelet concentration was identified when these dogs were subdivided by disease group (p = 0.133).

3.3 | Clinical manifestations of thrombocytopenia

One or more signs of bleeding, including gingival bleeding, hyphaema, epistaxis, petechiae, ecchymoses, haematemesis, melaena and haematuria, were present upon presentation in 26.9% of dogs (n = 206). Signs of bleeding were significantly associated with the disease category (χ^2 235.8, p < 0.001). The proportion of dogs with haemorrhage was highest in dogs with pITP (reported in 76.2% [109/143] of dogs) compared to the rest of the groups: 21.5% (44/205) of dogs diagnosed with a miscellaneous disease, 19.8% (19/96) of dogs with an infectious process, 10.9% (12/110) of dogs with inflammatory/immune-mediated disease and 10.6% (22/208) of dogs with neoplasia.

TABLE 1 Signalment of 762 dogs with thrombocytopenia from 7 referral institutions located in different UK geographic areas

Institution, region in the United Kingdom and number of dogs recruited	Institution 1 East 143 dogs	Institution 2 East 201 dogs	Institution 3 South-east 135 dogs	Institution 4 South-west 130 dogs	Institution 5 East 85 dogs	Institution 6 East Midlands 43 dogs	Institution 7 North-east 25 dogs
Median age (years)	5.6 (0.2–15.9)	7 (0.2–13.2)	7 (0.2–13)	7 (0.2–15.3)	7.2 (0.5–14)	6.8 (1.3–18.5)	6 (1–12.8)
Gender/neutering status							
Female	69/143 (48.3%)	93/201 (46%)	61/135 (45.2%)	69/130 (53%)	43/85 (50.6%)	25/43 (57.4%)	18/25 (72%)
Neutered	56	82	52	58	36	22	14
Entire	13	11	9	11	7	3	4
Male	74/143 (51.7%)	108/201 (54%)	74/135 (54.8%)	61/130 (47%)	42/85 (49.4%)	18/43 (42.6%)	7/25 (28%)
Neutered	60	79	49	49	35	12	5
Male	14	29	25	12	7	6	2
Breeds							
Spaniel breeds	27	52	38	27	22	14	8
Retrievers	35	42	31	27	12	8	3
Terriers	6	24	16	18	6	8	2
Sighthounds	4	6	6	8	6	1	2
Toy breeds	5	6	3	6	7	1	4
German Shepherds	16	10	7	3	1	1	0
Crossbreed dogs	38	13	10	5	5	5	0
Others	**12**	48	24	36	26	5	6
Travel history (outside the United Kingdom)	6/82 (7.3%)	8/143 (5.6%)	6/32 (18.8%)	3/127 (2.4%)	9/56 (16.1%)	0/45 (0%)	0/14 (0%)
Updated vaccinations	120/129 (93%)	149/168 (88.7%)	89/101 (88.1%)	97/120 (80.8%)	71/75 (94.7%)	44/45 (97.8%)	22/24 (91.7%)

Note: Breed categories were established to facilitate statistical analysis.

TABLE 2 Disease categories and subcategories of 762 dogs with thrombocytopenia in the United Kingdom

pITP	Cases	Neoplasia	Cases	Infectious	Cases	Inflammatory/immune-mediated	Cases	Miscellaneous	Cases
Total	143 (18.8%)	Total	208 (27.3%)	Total	96 (12.6%)	Total	110 (14.4%)	Total	205 (26.9%)
		Lymphoma	74	Bacterial	75	Pancreatitis	19	Drugs/toxins	63
		Sarcoma	33	Septic peritonitis	17	Non-associative IMHA/PIMA	15	Chemotherapy:	49
		Leukaemia	26	*Leptospira* spp.	9	Chronic enteropathy	14	Lomustine	11
		Carcinoma	15	Endocarditis	8	MUA/meningomyelitis	12	Vincristine	10
		MCT	13	Sepsis	7	Idiopathic IMPA	9	Melphalan	8
		Others	13	Bronchopneumonia	6	Lymphadenitis	6	Chlorambucil	5
		Undetermined	34	UTI/pyelonephritis	4	Multiple IM disease	8	Doxorubicin	5
				Osteomyelitis/discospondylitis	4	SRMA	4	Cytarabine and actinomycin D	3
				Abscess/fistulae	4	Chronic rhinitis	4	Carboplatin	2
				Cholangio-hepatitis	3	Chronic bronchopneumopathy	4	Cyclophosphamide	2
				Pyometra	3	Uveitis	3	Toceranib phosphate	1
				Pyothorax	3	Chronic hepatitis	3	Vinblastine	1
				Prostatitis	2	IM neutropenia	2	Rabacfosadine	1
				Campylobacter spp.	1	Others	7	Others	14
				Others	4			Renal	29
				Vector-borne	13			CRGV	16
				Ehrlichia spp.	6			CKD	9
				Borrelia spp.	1			AKI	4
				Leishmania spp.	4			Hepatobiliary	28
				Anaplasma spp. + *Ehrlichia* spp.	1			Undetermined	15

(Continues)

TABLE 2 (Continued)

pITP	Cases	Neoplasia	Cases	Infectious	Cases	Inflammatory/immune-mediated	Cases	Miscellaneous	Cases
				Leishmania spp. + *Ehrlichia* spp.	1			Vascular	8
				Parasitic	3			EHBO	5
				Viral	3			Neurological	24
				Fungal	2			IVDD	8
								CLM	7
								Epilepsy/MD	6
								Others	3
								Gastrointestinal	20
								AHDS	11
								GDV	3
								Gastric ulceration	2
								Others	4
								Trauma	9
								Coagulopathy	7
								Cardio-respiratory	6
								Bone marrow (undetermined cause)	6
								Vaccine-mediated	2
								Adder bite/bee sting	5
								Others	6

Abbreviations: AHDS, acute haemorrhagic diarrhoea syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; CLM, Chiari-like malformation; CRGV, cutaneous and renal glomerular vasculopathy; EHBO, extrahepatic biliary tract obstruction; GDV, gastric dilatation-volvulus; IM, immune-mediated; IMHA, immune-mediated haemolytic anaemia; IMPA, immune-mediated polyarthritis; IVDD, intervertebral disc disease; MCT, mast cell tumour; MUA, meningoencephalitis of unknown aetiology; PIMA, precursor-targeted immune-mediated anaemia; pITP, primary immune-mediated thrombocytopenia; SRMA, steroid responsive meningitis-arteritis; TP, thrombocytopenia.

3.4 | Haematological parameters among disease categories

Table 3 presents the haematological parameters identified to be significantly different in dogs diagnosed with pITP compared against the remainder of the disease categories. Dogs with pITP had a significantly lower automatic platelet concentration (8.00×10^9/L [IQR 13.00]) ($p < 0.001$) compared with all other disease category groups (Figure 1).

A significant relationship between disease group and anaemia ($p = 0.0006$), leucocytosis ($p = 0.0001$), mature neutrophilia ($p = 0.0001$) and the presence of a left shift ($p = 0.0001$) was also identified. Median haematocrit levels were significantly lower in dogs with pITP compared to dogs with infectious ($p = 0.031$), inflammatory/immune-mediated diseases ($p = 0.004$) or miscellaneous conditions ($p < 0.001$) but not in dogs with neoplastic ($p = 0.240$) disorders. Compared to dogs with neoplasia, dogs with pITP had higher white blood cell count, segmented neutrophil, band neutrophil counts and monocytes ($p < 0.05$). Furthermore, dogs with pITP had higher white blood cell counts, segmented neutrophil and lymphocytes than dogs with infectious disorders ($p < 0.05$).

The following differences were identified when the remainders of the disease categories were compared to each other: dogs with neoplasia had a lower haematocrit ($p < 0.001$), and higher white blood cell count ($p = 0.005$) than dogs within the miscellaneous diseases category and lower monocytes than dogs with inflammatory/immune-mediated diseases ($p = 0.010$); dogs with infectious diseases had higher band neutrophil ($p = 0.001$) and monocyte ($p = 0.030$) counts than dogs with within the miscellaneous category, and dogs with inflammatory/immune-mediated diseases had higher white blood cell ($p < 0.001$), segmented neutrophil ($p = 0.002$), lymphocyte ($p = 0.050$) and monocyte ($p < 0.001$) counts than dogs within the miscellaneous category.

3.5 | Platelet concentration as a predictor of causes of thrombocytopenia

ROC curve analysis showed significantly higher performance of platelet concentration for differentiation of dogs with pITP from other disease categories with an area under the ROC curve (AUROC) of 0.89 (95% CI 0.87–0.92) (Figure 2). The performance of platelet concentration for the diagnosis of neoplastic (AUROC = 0.53, 95% CI 0.49–0.58), infectious (AUROC = 0.48, 95% CI 0.42–0.53) and inflammatory/other immune-mediated (AUROC = 0.63, 95% CI 0.58–0.69) diseases was poor.

Using a cut-off value of 12×10^9, the specificity and sensitivity were 90% and 60%, respectively, for identifying dogs with pITP vs. other disease categories. A higher sensitivity of 92% for the exclusion of dogs with pITP was associated with a platelet concentration of $\geq 42 \times 10^9$/L, which was, on the other hand, poorly specific (69% specificity).

4 | DISCUSSION

This cross-sectional retrospective study describes the disease distribution of canine patients with thrombocytopenia in the United Kingdom. The highest proportions of dogs were diagnosed with neoplasia (27.3%), followed by miscellaneous causes (26.9%), pITP (18.8%), inflammatory/immune-mediated disorders (14.4%) and infectious diseases (12.6%). The platelet concentration in dogs with pITP was significantly lower (median 8×10^9/L, range: 0–70 $\times 10^9$/L) than dogs in the other four categories. The diagnostic performance of the degree of reduction of platelet concentration was appropriate for distinguishing pITP from other causes of thrombocytopenia (area under ROC curve = 0.89, 95% confidence interval 0.87, 0.92), with a platelet concentration $\leq 12 \times 10^9$/L being 60% sensitive and 90% specific.

To classify the dogs recruited we used broad aetiologic categories, similar to those established in previous studies (Botsch et al., 2009; Ellis et al., 2018; Grindem et al., 1991), although subgroups within some categories differed in this study to facilitate analysis. Furthermore, in the current study, only dogs where thrombocytopenia was validated by blood smear examination were included, and platelet clumping and the presence of comorbidities with the potential of also causing thrombocytopenia were exclusion criteria. Although the observation of a low number of clumps in the context of a disproportionally severe thrombocytopenia cannot reliably be associated with normal platelet numbers, these dogs were excluded to simplify data collection and analysis and to ensure that comparison among the disease categories was as accurate as possible.

The proportion of dogs in this UK population diagnosed with pITP was higher than previously reported (Cockburn & Troy, 1986; Botsch et al., 2009; Grindem et al., 1991). In the present study, a diagnosis of pITP was made on the basis of exclusion of other underlying causes and response to immunosuppressive treatment. In comparison, the most recent previous epidemiological study used additional criteria such as positive anti-platelet antibody testing (Botsch et al., 2009). It is possible that the higher proportion of pITP explains this difference, given that APA testing was performed in only one dog in our study population. The scarce use of this test in dogs nowadays is likely due to its limited availability in Europe. Furthermore, this assay is unable to accurately differentiate between primary and secondary ITP in dogs (Bachman et al., 2015; Dircks et al., 2009). A recent systematic review and meta-analysis of the utility of APA testing in pITP in humans concluded that this test is useful for ruling in an immune-mediated pathogenesis; however, the sensitivity was reported to be low (Vrbensky et al., 2019). An overestimation of pITP in our population is overall considered unlikely. Rather, in our cohort, cases that were thrombocytopenic in conjunction with a confirmed immune-mediated disease (i.e. 'Evans' syndrome, IMPA, SLE) were assigned to the inflammatory/immune-mediated disorders category, because, although it is possible that the thrombocytopenia in these dogs was a concurrent immune-mediated process, thrombocytopenia could also have resulted from consumption in the context of potential hypercoagulability, failure in thrombopoiesis

TABLE 3 Haematological parameters of 762 dogs diagnosed with thrombocytopenia in the United Kingdom and results of post hoc Dunn's test with a Sidák adjustment for multiple comparisons, showing significance of differences in haematological parameters between primary immune-mediated thrombocytopenia (pITP) and other disease categories associated with thrombocytopenia; significance level $p \leq 0.05$

		pITP (1) n = 143		Neoplasia (2) *n* = 208		Comparison between (1) and (2) Dunn's test	Infectious (3) *n* = 96		Comparison between (1) and (3) Dunn's test	Inflammatory/immune-mediated (4) *n* = 110		Comparison between (1) and (4) Dunn's test	Miscellaneous (5) *n* = 205		Comparison between (1) and (5) Dunn's test
	Ref. range[a]	Median	Range	Median	Range	*p*-value	Median	Range	*p*-value	Median	Range	*p*-value	Median	Range	*p*-value
Platelets ($\times 10^9$/L)	143–900	8.00	0.00–70.00	64.00	1.00–197.00	<**0.001**	60.00	0.00–188.00	<**0.001**	93.00	7.00–198.00	<**0.001**	109.00	0.00–199.00	<**0.001**
Presence of macrothrombocytes			25/76		93/167			34/87			48/99			85/161	
Haematocrit (%)	37.00–61.70	34.10	6.80–52.40	33.50	4.70–66.80	0.240	36.50	7.00–58.00	**0.031**	39.00	4.00–56.00	**0.004**	39.00	6.50–70.10	<**0.001**
White blood cells ($\times 10^9$/L)	4.90–22.00	15.35	1.57–133.87	11.38	0.17–194.50	**0.010**	11.36	0.11–83.60	**0.022**	13.48	1.71–96.69	0.283	9.75	0.36–66.50	<**0.001**
Segmented neutrophils (x10^9/L)	2.00–12.67	11.55	0.50–58.03	7.49	0.00–72.30	<**0.001**	8.64	0.01–74.40	**0.018**	9.83	0.08–75.00	0.156	6.24	0.01–79.21	<**0.001**
Band neutrophils ($\times 10^9$/L)	0.00–0.50	0.51	0.00–9.82	0.07	0.00–5.00	<**0.001**	0.56	0.00–4.12	0.356	0.49	0.00–18.50	0.290	0.00	0.00–6.65	<**0.001**
Monocytes ($\times 10^9$/L)	0.00–2.80	0.96	0.00–16.07	0.68	0.00–13.68	**0.004**	0.74	0.00–10.66	0.117	1.01	0.00–6.20	0.562	0.50	0.00–4.21	<**0.001**
Lymphocytes ($\times 10^9$/L)	0.50–5.10	1.65	0.16–132.53	1.43	0.00–163.38	0.102	1.36	0.06–8.90	**0.034**	1.69	0.00–8.22	0.575	1.23	0.05–13.05	<**0.001**
Eosinophils ($\times 10^9$/L)	0.00–1.49	0.10	0.00–2.08	0.07	0.00–4.24	0.136	0.05	0.00–3.56	0.228	0.14	0.00–7.66	0.294	0.10	0.00–1.44	0.749
Basophils ($\times 10^9$/L)	0.00–1.25	0.00	0.00–0.89	0.00	0.00–1.25	0.103	0.00	0.00–0.24	0.292	0.00	0.00–0.71	0.018	0.00	0.00–0.09	0.115

Note: 1: pITP, 2: neoplasia, 3: infectious, 4: inflammatory/immune-mediated and 5: miscellaneous.

[a]The reference range shown includes the lowest and highest limits of all ranges given by the different analysers used by the institutions.

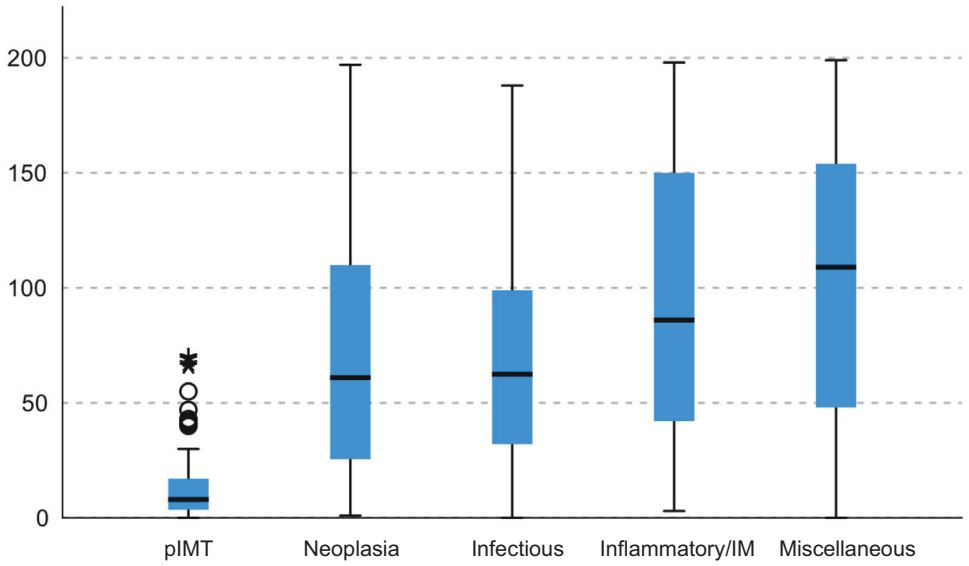

FIGURE 1 Comparison of automated platelet concentration values across different disease category groups in 762 thrombocytopenic dogs seen at seven UK referral centres. Boxes represent medians and interquartile ranges; whiskers represent the range and individual points the outliers. The automated platelet concentration was significantly lower ($p < 0.001$) in dogs with primary immune-mediated thrombocytopenia (pITP) compared to all other disease categories groups. IM, immune-mediated.

or splenic sequestration due to inflammation (Brooks, 2017; Feldman et al., 1988, Neel et al., 2014). However, this higher proportion of dogs with pITP may represent a relative increase due to vector-borne diseases being much less prevalent in this UK population. This hypothesis cannot be proven as the prevalence data of thrombocytopenia for the overall hospital populations at the different locations was not available. Additionally, it is also possible that the diagnosis of a vector-borne infection could have been missed in a subset of dogs given the fact that only 26.4% patients were tested.

The pITP group had the highest proportion of female dogs in our population, as demonstrated by comparable studies (Botsch et al., 2009; Grindem et al., 1991; Williams & Maggio-Price, 1984). In agreement with the results reported by Botsch et al., 2009, dogs with infectious diseases in our population were significantly younger, and dogs with neoplasia were older than dogs within the remainder of the aetiologic groups. Cocker spaniel dogs were common in our pITP category (32/143, 22.4%). A genetic contribution to the pathogenesis of pITP has been hypothesised, with Cocker spaniel dogs overrepresented in the disease demographics (Grindem et al., 1991, O'Marra et al., 2011). However, the Cocker spaniel breed is currently one of the most popular breeds in the United Kingdom (O'Neill et al., 2014; The Kennel Club, 2020), and one of the most commonly recorded breeds in our study (72/762, 9.40%). Our data were insufficient to ascertain if this hypothesis explained the marked difference in the prevalence of pITP compared to previous surveys conducted in other geographic locations.

Interestingly, a substantial body of literature supports an association between the severity of thrombocytopenia with a primary immune-mediated aetiology in small animals, and therefore, a higher likelihood of signs of bleeding (Botsch et al., 2009; Dircks et al., 2009; Ellis et al., 2018; Grindem et al., 1991; Neel et al., 2014; Putsche & Kohn, 2008); however, there is no published data about the utility of the platelet concentration to differentiate between causes of thrombocytopenia. The results of our ROC curve analysis support a hypothesis that severe thrombocytopenia is more likely to be indicative of pITP, with a platelet concentration cut-off value of $\leq 12 \times 10^9$/L being 90% specific for diagnosis. Haemorrhage was present at the time of admission in 76.4% dogs with pITP, and this proportion was similar to that reported in comparable studies, ranging from 70% to 81% (O'Marra et al., 2011; Putsche & Kohn, 2008). Severe thrombocytopenia was also documented in some dogs that were allocated in the remainder of the disease categories other than pITP. A component of immune-mediated platelet destruction is likely in these dogs, but concurrent pathophysiological mechanisms, including reduced platelet production and lifespan, platelet consumption due to DIC or chronic bleeding and splenic sequestration, are possible (Brooks, 2017; Feldman et al., 1988, Neel et al., 2014).

The prevalence of vector-borne diseases in our study differed greatly from that reported previously. Two previous studies out of Germany showed a prevalence of vector-borne disease linked to thrombocytopenia in 15.5%–20.5% of cases (Botsch et al., 2009; Dircks et al., 2009) compared to only 1.7% in our cohort. The prevalence of vector-borne disease in a thrombocytopenic dog population from the United States of America was also higher at 11% (Grindem et al., 1991). Overall, very few of the dogs included in our study were screened for an infectious disease where a travel history was not documented, which may have led to an under-estimation of vector-borne disease-related thrombocytopenia in this cohort. However, this difference is far more likely to reflect a low prevalence of tick-borne diseases in the United Kingdom. This notion is further supported by available information from Public Health England, and various veterinary studies, that confirm very low disease carriage

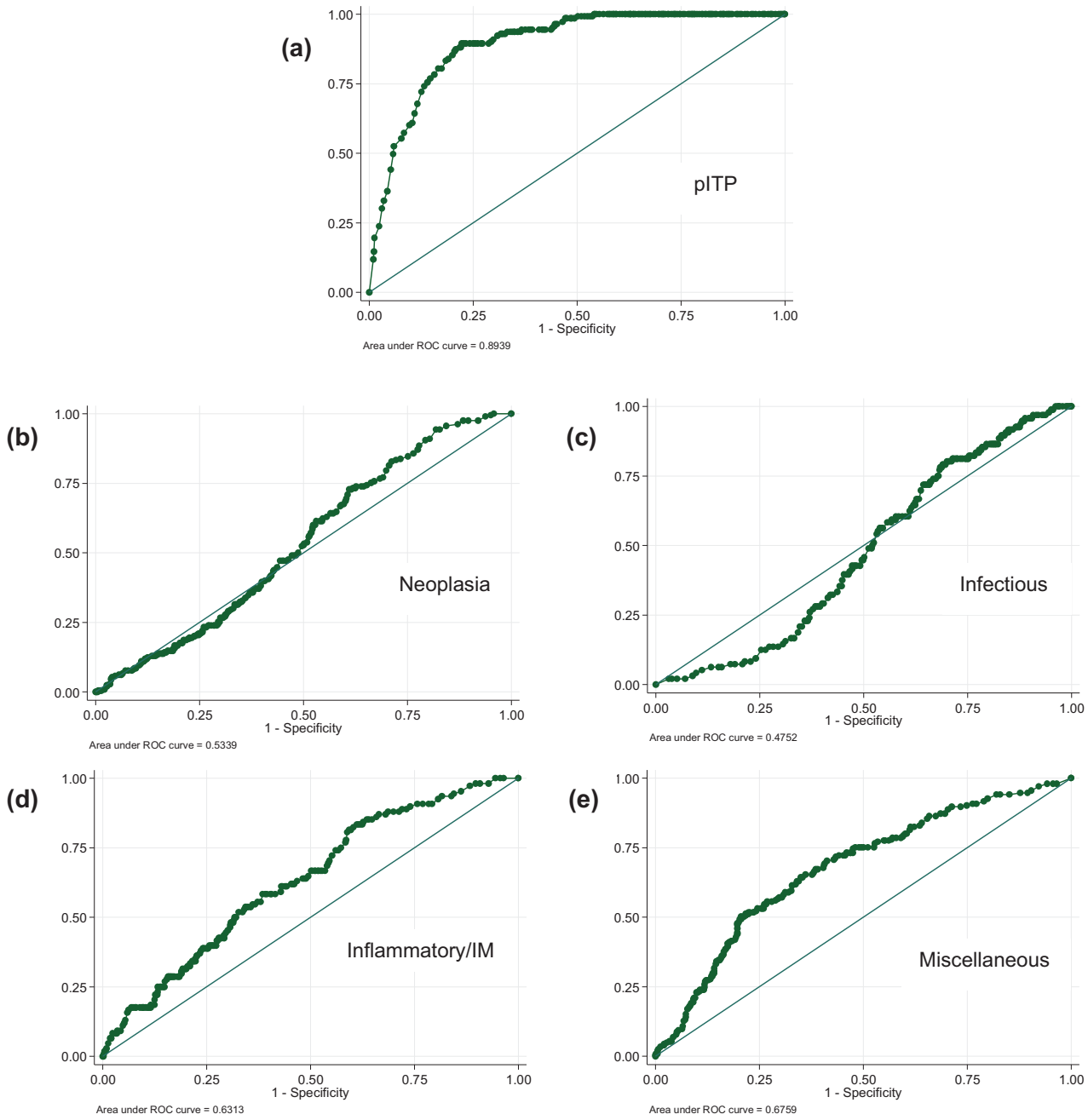

FIGURE 2 Receiver-operating characteristic curves of the five disease categories where the 762 thrombocytopenic dogs from seven UK referral centres where assigned. The cut-off value for platelet concentrations selected as a predictor of the diagnosis of primary immune-mediated thrombocytopenia (pITP) (a) was 12 × 109/L which had a specificity of 90% and a sensitivity of 60% (area under the ROC [AUROC] 0.89, 95% CI: 0.87–0.92). There was considerable overlap between the remainders of the groups (b–e) and were unable to identify a cut-off point at which platelet concentrations could reliably guide the diagnosis. IM, immune-mediated.

within the UK tick population (Medlock et al., 2018; Smith & Wall, 2013). Nevertheless, it is important to note that a recent study documented a marked increase in the prevalence of *A. phagocytophilum* from 0.74% to 4.60% between 2009 and 2015 (Keyte et al., 2021). Furthermore, in the last decade, there has been concern around some vector-borne diseases emerging in continental Europe and becoming established in United Kingdom due to optimisation of pet-friendly travel, increases in suburbanization and climate change-induced vector range expansion (Beugnet & Marié, 2009; Folly et al., 2020). Certainly, several case reports have described dogs becoming infected with *E. canis* (Wilson et al., 2013) and *Leishmania infantum* (McKenna et al., 2019) having never travelled outside the United Kingdom, and direct dog-to-dog transmission has been speculated. These data potentially highlight an increasing need to evaluate for vector-borne disease

potentially associated with thrombocytopenia despite a historically low prevalence.

There are a number of similarities between the haematological parameters of the disease categories in our population and those from comparable epidemiological studies. The prevalence of anaemia was previously reported to be higher in dogs with pITP, but these patients where categorised alongside other immune-mediated diseases, such as 'Evans' syndrome (Botsch et al., 2009; Grindem et al., 1991). In the present study, haematocrit levels were significantly lower in dogs with pITP compared to the remainder of the groups, excepting the neoplastic disorders category. Dogs with neoplasia had, however, a lower white blood cell count with lower neutrophil and monocyte counts, which was not reported in previous studies. Dogs with infectious disorders were more commonly neutropenic compared to other disease groups in previous studies, and dogs with infectious diseases in our population had lower white blood cell counts, segmented neutrophils and lymphocytes.

This study has several limitations, mainly due to its retrospective nature. First, although every effort was made to include only cases where sufficient information was available for classification, relevant data such as previous travel history, vaccination status or long-term follow-up was occasionally missing. Response to treatment and outcome was, however, collected in dogs with pITP, and this group underwent diagnostic testing to exclude other potential causes, leading to an excellent degree of confidence for this group. Second, there was no standardisation of the diagnostic protocols due to multiple clinicians from seven different referral centres being involved in the investigations of thrombocytopenia. However, each case was individually assessed by one author to ensure, to the best of our ability, that the conclusion drawn from diagnostics was appropriate. One particular limitation in this population was the categorisation of dog breeds with possible physiological thrombocytopenia, such as CKCS or Sighthounds (Brown et al., 1994; Sullivan et al., 1994). All included dogs with possible breed-related thrombocytopenia were diagnosed with a primary disease that also could have been associated with thrombocytopenia. Although evaluation for a mutation in the β1-tubulin gene could have been performed in a broader range of breeds than CKCS alone, this was not routinely performed, and in fact the only dog tested for this mutation was negative. In the absence of this information, prior haematology panels or repeat panels, once the illness resolved, could have helped in these cases but were not routinely available. We therefore could not exclude or confirm whether thrombocytopenia was definitively breed-related and therefore categorised cases on the assumption it was related to an underlying disease. The overall proportion of dogs in our cohort for which this potential exists however is minimal, particularly where these cases were distributed between several disease categories, with the largest proportion ending up in the miscellaneous category. It is therefore unlikely that this greatly impacted the results of the study.

Additional platelet parameters aside from platelet concentration, including MPV, platelet component (MPC), plateletcrit (PLC) and platelet distribution width, were not analysed in the present project as these were not included in all haematological panels of the referral centres. One previous study showed that the MPC and PLC were reduced in dogs with pITP compared with those with other diseases and control healthy dogs (Smith et al., 2014). However, there is controversy over whether dogs with pITP have an increased or decreased MPV as this is inconsistent in previous studies (Bommer et al., 2008; Dircks et al., 2009; Schwartz et al., 2014).

In conclusion, this retrospective study provides further evidence to support that markedly reduced platelet concentrations support a likely clinical diagnosis of pITP. The prevalence of thrombocytopenia associated with vector-borne diseases is lower in the United Kngdom compared to elsewhere in Europe or America.

AUTHOR CONTRIBUTIONS

Marina Martín-Ambrosio Francés: Data curation; Investigation; Project administration; Writing – original draft. Mayank Seth: Conceptualization; Supervision; Validation; Writing – review & editing. Mellora Jane Sharman: Supervision; Validation; Writing – review & editing. Danica Pollard: Formal analysis; Software; Validation; Writing – review & editing. Ana Liza Ortiz: Conceptualization; Validation. Rachel Louise Miller: Investigation; Validation; Writing – review & editing. Thomas Natsiopoulos: Investigation; Validation; Writing – review & editing. David J Walker: Investigation; Validation; Writing – review & editing. Bryn Jones: Investigation; Validation; Writing – review & editing. Barbara Glanemann: Investigation; Validation; Writing – review & editing

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflict of interest or arrangement with any company or organization.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. The research was approved by the ethical review committee at the Animal Health Trust (42-2018).

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