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The Prognostic Utility of Degenerative Left Shifts in Dogs

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Background: A degenerative left shift (DLS) in dogs is reported to be a poor prognostic indicator, but no studies have been reported to verify this claim.

Hypothesis/Objectives: To characterize the canine population affected by DLS and to determine if the presence and severity of the DLS are associated with increased risk of euthanasia or death.

Animals: Three-hundred and nineteen dogs with DLS (cases) and 918 dogs without DLS (controls) presented to the University of California, Davis Veterinary Medical Teaching Hospital between April 1, 1995 and April 1, 2010.

Methods: Retrospective case–control study. All cases had a CBC performed within 24 hours of presentation that showed an immature neutrophil count higher than the mature neutrophil count. Controls were matched by year of presentation and primary diagnosis. Survival analysis was used to determine the risk of death or euthanasia associated with DLS and other potential predictors.

Results: Half of cases versus 76% of controls were alive at discharge. Median in-hospital survival time was 7 days for cases and 13 days for controls. DLS was a significant predictor of death or euthanasia in both univariate and multivariate analysis (hazard ratio, HR, 1.9; 95% CI 1.54–2.34).

Conclusions and Clinical Importance: DLS in dogs is associated with an increased risk of death or euthanasia. This finding, however, varies with disease diagnosis and should be interpreted in light of the individual patient.

Key words: Complete blood count; Gastroenteritis; Neutrophils; Septic peritonitis; Survival.

Neutrophils play a fundamental role in the innate immune response, acting as the first line of cellular defense against microbial infection.[1] There also is a growing body of evidence to support the substantial contribution of neutrophils to the adaptive limb of the immune response by modulating both cellular and humoral immunity, particularly by the synthesis and release of immunoregulatory cytokines.[2–4] It is not surprising then that neutrophil kinetics and their role in disease have been extensively studied.

In health, the rate of neutrophil production and release equals the rate of neutrophil egress from the circulation. A functional storage compartment of neutrophils in the bone marrow of dogs affords a buffer to bridge any potential discrepancy between supply, the maximal capacity of which is fixed within physiologic limits, and peripheral utilization, which may vary dramatically. At normal rates of utilization, the marrow neutrophil reserve in dogs contains approximately a 5-day supply of cells.[5]

Increased demand for neutrophils depletes the marrow storage pool of mature neutrophils. Band neutrophils, or even earlier granulocytic precursors, then are released into circulation, and the leukogram is referred to as left-shifted.[5] A high neutrophil count with a left shift suggests that the bone marrow is able to respond to an inflammatory stimulus. In contrast, left shifts with normal or low neutrophil counts, despite stimulated granulopoiesis, suggest inability of the bone marrow to meet increased demand.[5–7]

A degenerative left shift currently, and most commonly, is defined by the number of immature neutrophils exceeding the number of mature neutrophils in circulation and implies that demand for neutrophils from an inflammatory nidus is exceeding granulopoietic capacity.[6–10] It is commonly stated, in veterinary literature, that a degenerative left shift carries a grave prognosis in dogs and other animals with a large storage pool of neutrophils.[6–10] To the authors' knowledge, no studies have been undertaken to investigate this claim. The objectives of this study were to characterize the canine population with degenerative left shifts that presented to a large veterinary teaching hospital and to determine if the presence and severity of the degenerative left shift were associated with a higher risk of euthanasia or death. We hypothesized that a degenerative left shift would not be associated with an increased risk of euthanasia or death.

Abbreviations:

CBC	complete blood count
DLS	degenerative left shift
N/I	mature neutrophil to immature neutrophil ratio
VMACS	Veterinary Medical and Administrative Computer System

Materials and Methods

An electronic medical records database (Veterinary Medical and Administrative Computer System [VMACS]) was used to retrospectively review medical records for dogs having an initial CBC performed within 24 hours of presentation to the William

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R. Pritchard Veterinary Medical Teaching Hospital at the University of California, Davis between April 1, 1995 and April 1, 2010. Patients were included as cases if their initial CBC showed evidence of a degenerative left shift (DLS), defined as the sum of immature neutrophils exceeding the sum of mature neutrophils. Only results of the first CBC were included in the analyses. Exclusion criteria included the presence of a mature neutrophil count equal to or greater than the sum of immature neutrophils, confirmation of Pelger Huet anomaly,[11,12] an uncertain disease diagnosis, an incomplete medical record, and treatment with chemotherapeutic agents within 1 month of presentation.

Using VMACS, medical records then were searched for the control group. Controls were included if a CBC was performed within 24 hours of hospitalization, but a DLS was never observed throughout the entire hospital stay. Exclusion criteria included an uncertain disease diagnosis and an incomplete medical record. After review of the records, a random number generator[13] was used to select 3 controls per case, as possible, matching on final diagnosis and within 1 year of the case presentation. Three controls per case were selected to improve study power and efficiency; beyond 3 controls, gains in these parameters are negligible.[14]

Data retrieved from the medical records included signalment (age, sex, neuter status, and breed), whether or not prior treatment had been undertaken, clinical diagnoses, CBC results, hospitalization duration, and discharge status (alive, dead, or euthanized). Data from the CBCs included total white blood cell, mature neutrophil, band neutrophil, metamyelocyte, promyelocyte, and myelocyte counts, as well as numbers of unclassifiable cells. From April 1, 1995 to September 1, 2001, hematological parameters were analyzed using a Baker Systems 9110 Plus Hematology Analyzer[a] and from September 1, 2001 to April 1 2010, hematological parameters were analyzed using an ADVIA 120 Hematology System[b] using the species-specific setting in the MultiSpecies System Software.[c] Manual leukocyte differentials of 200 cells were performed on all blood smears by technicians and clinical pathologists. All clinical pathologists reviewing slides were diplomates of the American College of Veterinary Pathologists and all technicians were licensed clinical laboratory scientists within the State of California. Laboratory classification of granulocytic precursors is based on guidelines previously published in veterinary books.[15,16]

Statistical Analysis

Descriptive statistics were performed for all variables. Pearson's chi-squared test was used to assess predictor variables for independence. The main predictor variable was DLS; however, additional predictor variables to assess neutrophil kinetics were evaluated, including total neutrophil count (neutrophilia, normal neutrophil count or neutropenia) and an indicator for shift severity (presence or absence of earlier neutrophil precursors [metamyelocytes, myelocytes, promyelocytes]). Potential confounding predictor variables included age category (≤3 years, >3 to ≤6 years, >6 years to ≤9 years, and >9 years), sex, previous treatment status, breed size category (≤15 kg, >15 kg to ≤30 kg, and >30 kg), neuter status, and disease diagnosis. For breed size categories, American Kennel Club average breed weight classifications were used, and cut-off values were chosen to balance biological and sample size considerations among categories. For mixed breeds, category was based on primary breed description. For example, "shepherd mix" was placed in the German Shepherd Dog category. Additionally, disease diagnosis was analyzed in 2 ways: (1) by categorizing the broad diagnosis in regard to anatomic location or body system (as described in Table 1), or (2) by the most common, specific disease diagnoses, which included pneumonia, septic peritonitis, gastroenteritis, wounds, parvoviral enteritis, immune-mediated neutropenia, and pancreatitis.

Table 1. Descriptive statistics describing study variables for dogs with (cases) and without (controls) DLS.

Variable	Overall Count (%)	Cases (N = 319)	Controls (N = 918)
Sex			
Male	611 (49%)	159 (50%)	452 (49%)
Female	626 (51%)	160 (50%)	466 (51%)
Neuter status			
Yes	837 (68%)	216 (68%)	621 (68%)
No	400 (32%)	103 (32%)	297 (32%)
Discharge status			
Dead/euthanized	370 (30%)	152 (48%)	216 (24%)
Alive	867 (70%)	167 (52%)	702 (76%)
DLS			
Present	319 (26%)	319 (100%)	0
Absent	918 (74%)	0	918 (100%)
Neutrophil count category			
Neutropenia	388 (31%)	244 (76%)	144 (16%)
Normal neutrophil count	386 (31%)	60 (19%)	326 (35%)
Neutrophilia	463 (37%)	15 (5%)	448 (49%)
Shift severity			
Precursor absence	199 (16%)	177 (55%)	861 (94%)
Precursor presence	1038 (84%)	142 (45%)	57 (6%)
Disease group			
Thorax	311 (25%)	78 (24%)	233 (25%)
Abdomen	579 (47%)	150 (47%)	429 (47%)
Integument	193 (15%)	50 (16%)	143 (15%)
Immune	110 (9%)	30 (9%)	80 (9%)
Cancer	44 (4%)	11 (3%)	33 (4%)
Previous treatment			
Yes	531 (43%)	137 (43%)	394 (43%)
No	706 (57%)	182 (57%)	524 (57%)
Breed/size			
Small (≤15 kg)	339 (28%)	106 (33%)	233 (25%)
Medium (>15 to ≤30 kg)	549 (44%)	122 (38%)	427 (47%)
Large/giant (>30 kg)	349 (28%)	90 (29%)	258 (28%)
Hospital days			
Range (average)	1–42 (3.7)	1–23 (4.16)	1–42 (3.58)
Age in years, continuous			
Range (average)	0.1–18 (6.7)		
Age in years, categorical			
<3	276 (22%)	76 (24%)	200 (22%)
3–6	244 (20%)	77 (24%)	167 (18%)
6–9	258 (21%)	60 (19%)	198 (22%)
≥9	459 (37%)	106 (33%)	353 (38%)

By categorizing the mature neutrophil to immature neutrophil ratio (N/I) into quartiles (cut points at 0.35, 0.56, and 0.80; range, 0.2–1) among the DLS cases, trends for increasing hazard of death or euthanasia with increase in severity of DLS were analyzed. The main statistical approach was survival analysis, using days of hospitalization as the time-to-event variable and death or euthanasia as the event of interest (versus alive at the time of discharge). Univariate survival analysis was conducted using the

Kaplan–Meier method, and statistical significance between groups was assessed using the log-rank test. Multivariate survival analysis was performed using the Cox proportional hazards model by including statistically significant variables and those thought to be of biological importance and calculating hazard ratios and 95% CI. Additionally, the Akaike Information Criterion (AIC) was used to measure goodness-of-fit estimated statistical models.[17] Validity of the proportional hazards assumption was determined by chi-square testing of scaled Shoenfeld residuals.[18] Variables with *P*-values ≤.05 were considered statistically significant. All analyses were conducted using R version 2.11.1.[19]

Results

Five hundred twenty-five dogs were identified as potential cases based on the initial database search for patient CBCs in which immature granulocytes exceeded mature neutrophil counts. Of these 525 potential cases, 206 dogs were excluded from the study. The majority of dogs were excluded because the mature neutrophil count equaled or exceeded that of immature neutrophils (n = 154), either upon review of unclassifiable cells (n = 149) or because of the finding of a Pelger Huet anomaly (n = 5) after review of the blood smears. Other causes of exclusion included chemotherapy within 1 month of presentation (n = 39) and incomplete medical records or multiple disease diagnoses (n = 13). A total of 319 dogs therefore were included as cases in the study, and 918 dogs were selected for the control group.

Descriptive data are summarized in Table 1. Average ages were similar between both cases (6.6 years; range, 0.1–18) and controls (6.8 years; range, 0.1–17) as were hospitalization times: 4.2 days (range, 1–23) and 3.6 days (range, 1–42), respectively. For the categorical variables, sex and prior treatment appeared to be fairly evenly distributed between cases and controls. However, there was a notable difference in the overall percentage of death or euthanasia between cases and controls: 48% (n = 154/319) for patients with DLS but only 24% (n = 216/918) for controls. Additionally, 45 specific diagnoses were identified (Table 2), but 71% of cases were accounted for by the following 7 diseases: pneumonia (n = 62), septic peritonitis (n = 48), gastroenteritis excluding parvoviral enteritis (n = 34), skin wounds (n = 23), parvoviral enteritis (n = 20), immune-mediated neutropenia (n = 20), and pancreatitis (n = 19).

Pearson's chi-squared tests indicated potential nonindependence of diagnosis group from age category ($P < .01$) as well as nonindependence of DLS from both neutrophil count ($P < .001$) and shift severity ($P < .001$). Univariate survival analyses identified 6 significant predictors of outcome. These included DLS status (which was the strongest predictor [$P < .001$]), neutrophil count ($P < .001$), shift severity ($P < .001$), age ($P < .001$), broad diagnosis group ($P < .001$), and neuter status ($P = .005$). Time-to-event analysis indicated that median in-hospital survival time for dogs with DLS was 7 days, whereas that of the control group was 13 days ($P < .001$). A summary of log-rank results is given in Table 3, and the Kaplan–Meier curve (Fig 1) graphically displays the difference for in-hospital survival probabilities over time between patients with DLS and controls. Investigation of the 7 specific disease diagnoses showed no significant difference between the presence or absence of DLS in patients with pneumonia and wounds. Additionally, within the case population, comparing outcomes by neutrophil count category or shift severity group showed no significant effect ($P = .13$ and $P = .47$, respectively).

Trend analysis to evaluate increased hazard of death or euthanasia with increase in severity of DLS was performed using the most severe N/I ratio category (0.02–0.35) as the reference (summarized in Table 4).

Table 2. Disease diagnoses represented by the canine case (with DLS) and control (without DLS) populations in this study and their broad categorizations by anatomic location or body system.[a]

Body System	Disease Diagnosis
Thorax	Pneumonias
	Pyothorax
	Acute respiratory distress syndrome
	Endocarditis/pericarditis
	Lung lobe torsion
Abdomen	Bile duct obstruction
	Dystocia
	Gastritis/enteritis
	Gastrointestinal foreign body
	Hepatopathy
	Pancreatitis
	Parvoviral enteritis
	Pyelonephritis
	Pyometra
	Retroperitoneal abscess
	Septic peritonitis
Integument	Abscess
	Bite wound
	Cellulitis
	Burns
	Degloving injuries
	Erythema multiforme
	Mastitis
	Necrotizing fasciitis
	Neutrophilic dermatitis
	Skin ulcerations/wounds
	Generalized demodecosis
	Wound dehiscence
Immune	Immune mediated hemolytic anemia (IMHA)
	Immune mediated neutropenia (IMN)
	Immune mediated thrombocytopenia
	Evan's syndrome
	Immune mediated vasculitis
Cancer	Acute leukemia
	Acute lymphoblastic leukemia
	Acute myeloid leukemia
	Bronchogenic carcinoma
	Large granular lymphoma
	T cell lymphoma
	Multiple myeloma

[a]Disease diagnoses without controls obtained are omitted: cryptococcus meningitis, neutrophilic glossitis, pyogranulomatus meningitis, septic bursitis, and tooth root abscess.

Table 3. Results of univariate survival analyses, including the log-rank chi-square test statistics and *P*-values for significant predictor variables for specific diagnoses within the canine study population.

Variable	Variable Sub category	χ^2 Value	*P*-Value
DLS		38.3	<.001
Shift severity		27	<.001
Neutrophil count		21.4	<.001
Age category		22.4	<.001
Neuter status		7.7	<.01
Diagnosis group		21.3	<.001
	Immune	14.2	<.001
Specific diagnosis		75.3	<.001
	Septic peritonitis	47.9	<.001
	Parvoviral enteritis	10.8	<.01
	IMN	14.4	<.01
	Gastroenteritis	8.5	<.01
	Pancreatitis	4.7	.031

χ^2 value, chi-squared value for log-rank test; IMN, immune-mediated neutropenia.

Although 2 of the 3 categories showed a trend of decreased hazard of death or euthanasia when compared to the highest severity reference category, the overall test for trend was nonsignificant (*P* = .12).

Multivariate survival analysis performed with the Cox proportional hazards model showed similar, but not identical, results to the univariate analysis (shown in Table 5). DLS and shift severity were assessed as outcome predictors in separate multivariate models because they were highly correlated. In separate models, DLS remained a significant predictor of death or euthanasia (HR, 1.90; 95% CI, 1.54–2.34; *P*-value, <.001) as did shift severity (HR, 1.74; 95% CI, 1.37–2.2; *P*-value, <.001), although DLS had a larger HR and a narrower CI. When included in the same model, DLS remained a significant predictor, though shift

Table 4. Summary of results of the test for trend in outcome with decreasing severity of DLS in canine case population, as measured by the mature/immature neutrophil ratio (N/I) index.[a]

N/I level	n	HR	SE (coef)	*P*-Value
0.02–0.35[a]	80			
0.35–0.56	78	0.62	0.23	.044
0.56–0.80	81	0.77	0.22	.220
0.80–0.97	80	0.61	0.23	.031
	Overall: Likelihood Ratio Test = 6.64			.115

[a]The 0.02–0.35 N/I level is the referent level; HR, hazard ratio; SE, standard error; n, sample size for each quartile.

Table 5. Summary of multivariate survival analysis results from the optimized Cox proportional hazards model including all variables that were significant predictors of death/euthanasia in the canine study population.

Variable	HR	95% CI	*P*-Value
DLS	1.90	(1.54, 2.34)	<.001
Age category	1.22	(1.11, 1.34)	<.001
Septic peritonitis	2.01	(1.60, 2.54)	<.001
Gastroenteritis	0.59	(0.36, 0.96)	.033

HR, hazard ratio; CI, confidence interval; DLS, degenerative left shift.

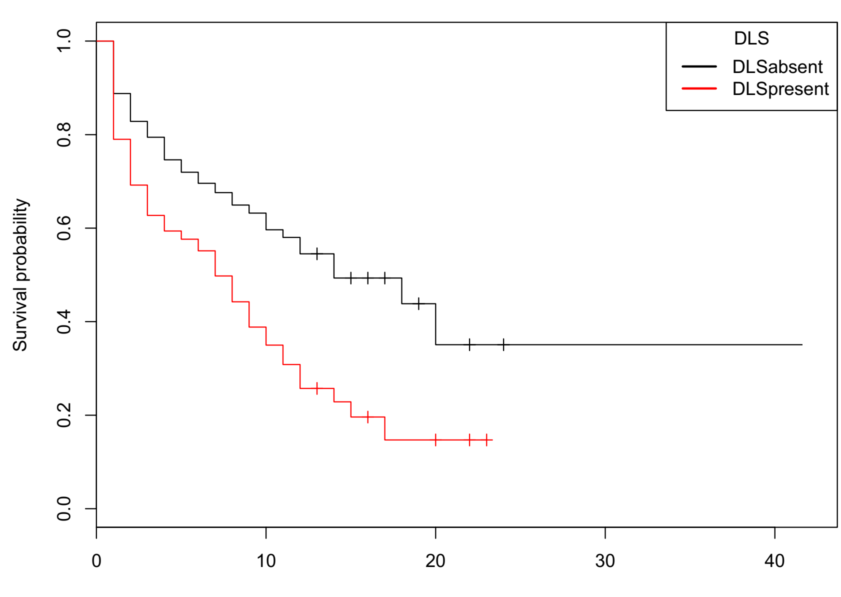

Fig 1. Kaplan–Meier curve demonstrating survival after hospital admission for dogs based on DLS status. DLSpresent line represents cases (bottom curve) and DLSabsent line represents controls (top curve). Median survival time is 7 days for cases, 13 days for controls (*P*-value <.001).

severity was no longer significant. Additionally, overall, the model using DLS as the sole outcome predictor had the best model fit as reflected by the lower AIC value; thus, DLS was kept in the final multivariate regression model, whereas shift severity was not. Age category remained a significant predictor (HR, 1.22; 95% CI, 1.11–1.34; *P*-value, <.001), but treatment was shown to be nonsignificant. The more significant of the diagnostic categorizations (anatomic location or body system versus. specific diagnosis) was the specific diagnosis, thus only this variable was included in the model to avoid overparameterization. Of this group, 2 specific diagnoses, septic peritonitis (HR, 2.03; 95% CI, 1.61–2.56; *P*-value, <.001) and gastroenteritis (HR, 0.59; 95% CI, 0.36–0.97; *P*-value, .036) were significant outcome predictors. Addition of interaction terms to the model did not improve the fit of the model or result in a notable change to effect measures, and thus were not included in the final model.

Discussion

This study indicates that hospitalized dogs with DLS have nearly 2-fold risk of death or euthanasia as compared to those without DLS after adjusting for total neutrophil count, degree of left shift, age category, sex, neuter status, previous treatment, breed size category, and disease diagnosis. Age category remained a significant predictor, and one would expect older animals to be at an increased risk of death or euthanasia. Age often is strongly related to disease and mortality rates in epidemiological models, and thus was retained in the final multivariate model. Additionally, disease diagnoses were quite variable as outcome predictors. For example, no significant difference in outcome was found within the pneumonia and wounds cases when compared to their corresponding controls, whereas 2 specific diagnoses, septic peritonitis (HR, 2.03; 95% CI, 1.6–2.6) and gastroenteritis (HR, 0.59; 95% CI, 0.36–0.97), remained significant predictor variables in each analysis. The presence of septic peritonitis resulted in a 2-fold increase in risk of death or euthanasia, whereas the presence of gastroenteritis counterintuitively had a seemingly protective effect for animals with DLS. Given the size of the gastroenteritis group, 20 cases, this protective effect might be an artifact of small sample size and not arise in studies including more cases with this diagnosis. Additionally, even the more specific diagnoses were clinical diagnoses and broad with respect to their potential etiologies. Therefore, although a DLS does confer a poor prognosis for in-hospital survival overall, the disease diagnosis may have a stronger impact on outcome and therefore play a larger role in informing clinical decisions.

Pearson's chi-squared testing indicated nonindependence of the broad, anatomic location or body system diagnosis variable and age category. Upon closer examination of the specific diseases, this was not surprising. For example, parvovirus is most common in puppies. When included in multivariate analyses, however, the broad diagnosis variable was not a significant predictor of outcome. Additionally, DLS, neutrophil count, and shift severity all were highly correlated with one another. This makes sense biologically because they each are measures of the degree of change in neutrophils and their precursors, and therefore take into account similar information for each animal. Upon detailed analysis of each variable, DLS remained the strongest predictor of outcome and generated the best model fit for the data in this study.

Given the retrospective nature of this study, there are a number of limitations to consider. First, many different technicians and clinical pathologists reviewed the blood smears on which DLS was diagnosed, which could lead to observer bias over time. Second, the distinction between band and segmented neutrophil can be ambiguous and may have affected the classification of patients with similar band and segmented neutrophil counts. Third, disease diagnoses often were based on clinical judgment rather than a diagnostic gold standard. Thus, standardization in diagnoses across cases and clinicians was difficult.

Cases of acute myelogenous leukemia were retained in the data set. These were acute leukemias with large numbers of blast cells in circulation that were not included as immature granulocytes. Also, 2 of the 3 cases had only bands seen as the immature granulocytes, with no maturational gradient that would be expected with differentiation of neoplastic blast cells. Therefore the left shift more likely was because of the inflammatory cytokine release (eg, TNF-α) from the neoplastic cells, rather than dysplasia in the neoplastic cell line creating bands. Thus, these cases were kept in the analysis.

It is unknown how many patients seen by the hospital may have had DLS without having a CBC performed, and we cannot be certain that our case population is representative of the true DLS population. Furthermore, because the results of this study are restricted to dogs presenting at the UC Davis Veterinary Teaching Hospital for a subset of possible disease diagnoses, the generalizability of the results must be considered. Another limitation to the study is the difficulty in adequately identifying potential confounders of the DLS-survival relationship, both because of the limitations of data available retrospectively and the difficulty in identifying all factors that could have affected survival. An important example includes owner characteristics, such as disposable income available for treatment and willingness to treat, neither of which were measurable in this study. Also, clinician attitudes about DLS may have impacted patient management and case outcome. Considering that DLS previously has been reported to carry a poor prognosis,[6–10] the findings in this study may reflect preconceived clinician perceptions of prognosis. Although median hospitalization times were similar for cases and controls, and median hospital survival of 7 days may suggest treatment despite DLS, this potential confounding factor must be considered.

Interestingly, we did not detect a trend in severity of DLS and hazard of death or euthanasia. However, 2 of the 3 categories showed some reduction in hazard with less severe N/I ratios. An analysis with larger sample sizes, allowing for a more finely stratified analysis of trend, might yield different results. Also, many methods have been used to estimate the severity of a left shift in humans, and these are used predominantly in neonatal and pediatric medicine. The N/I index used for DLS in our study was based on the most accurate methods described in both canine and neonatal human patients,[20] but it still is only an estimate of severity. It is a ratio of mature to immature cells and does not take into account the total number of leukocytes. Also, the severity of left shift (presence versus absence of granulocytic precursors more immature than bands) did not have a significant effect on outcome.

Consideration of the total number of leukocytes also may be applied to the definition of DLS used in this study. Most references define DLS as immature cells exceeding mature.[6–8] Controversy exists about this definition, mainly because it does not take into account the overall number of leukocytes. For example, a DLS with neutrophilia is very different from DLS with leukopenia. However, when the overall neutrophil count was assessed within the DLS case population, it was not found to be a significant predictor of outcome. In summary, although a single definition is required for simplicity and analysis, critical evaluation of bone marrow kinetics in each individual patient should be considered.

Conclusion

This study shows that, even after accounting for confounding variables, dogs with DLS are 1.9 times more likely to either die or be euthanized in the hospital than those without DLS. When individual disease diagnoses were investigated, significant differences in hazard were not found in all categories. Additionally, certain diseases (eg, septic peritonitis, gastroenteritis) affected patient outcome regardless of DLS status and other confounders. When interpreting these findings, the individual patient and specific disease diagnosis should be taken into consideration. Prospective studies with larger number of patients in individual disease categories may be helpful to further characterize the effect of DLS in dogs and better understand its potential usefulness as a prognostic indicator.

Footnotes

[a] BioChem ImmunoSystems Inc, Allentown, PA
[b] Siemens Healthcare Diagnostics Inc, Tarrytown, NY
[c] Siemens Medical Solutions Diagnostics Inc, Tarrytown, NY

Acknowledgments

Conflict of Interest Declaration: Authors disclose no conflict of interest.

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