

Outcome and Prognostic Factors for Canine Splenic Lymphoma Treated by Splenectomy (1995–2011)

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Objective: To assess the outcome of canine splenic lymphoma treated with splenectomy and to evaluate prognostic factors, including involvement of other sites, adjuvant chemotherapy, and the effect of World Health Organization (WHO) histological classification of canine malignant lymphoma.

Design: Multi-institutional, retrospective study.

Animals: Client-owned dogs (n = 28).

Methods: Medical records (1995–2011) of dogs with a histological diagnosis of splenic lymphoma and treated by splenectomy submitted by Veterinary Society of Surgical Oncology members were reviewed. Included were dogs treated with or without adjuvant therapy. Overall survival, disease-free interval, and cause of death were determined. Prognostic factors and the WHO histological classification of canine malignant lymphoma were evaluated with respect to outcome.

Results: Dogs with splenic lymphoma treated by splenectomy had a 1-year survival rate of 58.8%, after which no animals died of their disease. B cell lymphoma held a better prognosis for survival than other variants of splenic lymphoma. Marginal zone lymphoma and mantle cell lymphoma were the most common B cell lymphoma subtypes in our study. Hemoabdomen and clinical signs related to splenic lymphoma, including abdominal distention, lethargy, and anorexia, were poor prognostic indicators, whereas disease confined to the spleen was a positive prognostic indicator. Pre- or postoperative adjuvant chemotherapy did not provide a survival benefit.

Conclusion: Based on our sample population, splenectomy alone was an effective treatment for splenic lymphoma in cases with disease confined to the spleen. Chemotherapy may not improve survival in cases of lymphoma restricted to the spleen.

Little is known about the clinical outcome of dogs with primary splenic lymphoma. Past studies report different forms of lymphoma,^{1,2} including cases involving the spleen; however, only 3 reports describe canine primary splenic lymphoma and its outcome.^{3–5} There are few outcome data following splenectomy for the treatment of splenic lymphoma. Splenectomy can be performed in the cases of lymphoma before diagnosis because of splenic rupture leading to a hemoabdomen or to diagnose the cause of splenomegaly or a splenic mass. In cases of lymphoma, splenectomy can be used to decrease disease burden or to treat cases unresponsive to chemotherapy.³ As is the case in human primary splenic lymphoma, recent veterinary studies^{4–6} suggest that splenectomy should be considered part of the treatment protocol for splenic lymphoma.^{6–10}

The diagnosis and classification of splenic lymphoma is based on histopathological characteristics and immunohistochemistry. Recently, the American College of Veterinary

Pathologists Oncology Committee published a report applying the World Health Organization (WHO) system of human lymphoma classification to canine lymphoma.¹¹ Use of this histopathological classification system may help with the prognostication of splenic lymphoma of the spleen and other sites. There are 43 different types of T and B cell lymphomas as adapted from the WHO classification system.¹¹ Lymphoma classifications that are relevant to splenic lymphoma from this system include marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), large diffuse B cell lymphoma, follicular lymphoma, peripheral T cell lymphoma (not otherwise specified), and natural killer cell lymphoma.¹¹

Using this WHO classification system for canine lymphoma,¹¹ 2 retrospective case series^{5,6} investigating outcome in canine splenic MZL, suggested this form of canine lymphoma may have of a more indolent course of disease than other forms of lymphoma.^{4,5} MZL is considered an indolent form of lymphoma in humans if confined to the spleen, and

splenectomy is therefore thought to result in long-term remission and in most cases is even curative.^{6–8} Based upon these studies, the predictive value of the WHO classification for canine lymphoma and whether splenectomy alone (without adjunctive chemotherapy) may suffice in cases of canine splenic lymphoma suggests that further investigation into how these classifications may apply to the canine population is indicated.

The objectives of our study were to evaluate the overall outcome for canine lymphoma treated with splenectomy, prognostic factors, and the prognostic value of the WHO histological classification for canine splenic lymphoma. We hypothesized that adjuvant chemotherapy would not provide a survival benefit in dogs with splenic lymphoma treated with splenectomy, the extent of the disease would be predictive of survival, and that the WHO histological classification for canine lymphoma would be predictive of survival.

MATERIALS AND METHODS

Members of the Veterinary Society of Surgical Oncology (VSSO) were asked to submit cases via the VSSO-Listserv. Inclusion criteria were dogs that underwent a splenectomy with a histological diagnosis of splenic lymphoma from 1995 to 2011. When available, histopathology was reviewed by 1 pathologist (TS), immunohistochemistry was performed, and the splenic lymphoma was classified according to the WHO classification system. Information acquired for each case included signalment, presenting complaint, reason for surgical intervention, histological diagnosis and classification (including immunohistochemistry for T cell [CD3] and B cell [CD79a] receptors), preoperative treatment and staging performed, postoperative treatment, disease-free interval (DFI), overall survival time (OST), and cause of death. DFI was defined as the number of days between splenectomy and first relapse when full remission was obtained with surgical treatment and/or chemotherapy. OST was defined as the number of days between splenectomy and death. Prognostic factors evaluated included age, sex, breed, presenting complaint, preoperative thrombocytopenia, preoperative anemia, stage and extent of disease, the presence or absence of perioperative disseminated intravascular coagulation (DIC), chemotherapy (pre- and/or postoperative), histological classification, and duration of first remission expressed as DFI. Preoperative staging tests performed for all dogs included abdominal ultrasound, thoracic radiographs (2 or 3 views), and fine needle aspiration of any enlarged lymph nodes. Postoperative staging was not performed on a regular basis in all cases.

When available, 4 unstained slide preparations or whole fixed tissue samples embedded in paraffin were submitted for histopathology and immunohistochemistry. Histology equipment and supplies were obtained from Dako, Inc. (Carpinteria, CA) unless otherwise noted. Sections were deparaffinized and heat-mediated antigen retrieval performed (Envision FLEX Target Retrieval Solution, High pH) in a computer-controlled

water bath (PT Link) at 97°C for 30 minutes. Immunohistochemistry was performed using an automated immunohistochemistry processor (Cytomation Autostainer Plus). Endogenous peroxidase activity was blocked by incubation in hydrogen peroxide solution for 30 minutes (EnVision FLEX Peroxidase-Blocking Reagent). Tissue sections were incubated with diluted (Envision FLEX antibody diluent) primary antibody for 30 minutes at room temperature (rabbit polyclonal anti-human CD3 and mouse monoclonal anti-human CD79a [Clone HM57]; 1:400). A goat anti-mouse/rabbit IgG and horseradish peroxidase-tagged polymer system (EnVisionFLEX/HRP) were used for detection, and staining developed (EnVision FLEX DAB+ Chromogen) and counterstained with hematoxylin. Negative controls were performed by replacing primary antibody with dilution buffer alone. Splenic lymphomas were classified according to the WHO system of classification of canine lymphomas.^{3,12}

Statistical Analysis

Prognostic factors for OST and DFI were evaluated using univariate and multivariate analyses followed by multivariate logistic regression analysis and included age, sex, breed, presenting complaint, stage and extent, treatment with adjuvant chemotherapy, histological classification, and duration of first remission (SPSS Statistics v22.0, IBM Corporation, Armonk, NY). Prognostic variables for outcome were individually assessed in the univariate analysis and variables with $P < .20$ were subsequently included in the multivariate analysis, with a backward elimination procedure. Results for DFI and median survival time were censored for dogs that died of causes other than lymphoma, were lost to follow-up, and were still alive at the end of the accrual period. Kaplan–Meier/log rank analysis was performed to estimate survival and disease-free intervals.

RESULTS

Forty-one dogs were included in this study. Breeds included were mixed breed ($n = 5$), Cocker Spaniel, Shih Tzu, Rottweiler (3 each), Golden Retriever, English Springer Spaniel, German Shepherd, French Bulldog, Fox Terrier, Border collie (2 each), and 1 each of 15 other breeds. There were 9 intact males, 9 castrated males, 5 intact females, and 18 spayed females. Median weight was 15.0 kg (range 5–48 kg). Presenting complaints included lethargy (15 dogs), anorexia/decreased appetite (8), abdominal distention (7), weight loss (7), vomiting (6), diarrhea (5), and polyuria/polydipsia (5). Fourteen cases had no clinical signs at the time of diagnosis, because most of these cases were diagnosed only at a routine checkup or neuter ($n = 12$).

Of the 41 total dogs, 15 were still alive at the end of the accrual period and 1 was lost to follow-up at 234 days post-splenectomy. Of 6 dogs that died, 2 died of causes related to their disease. Of 19 dogs euthanized, 13 were euthanized because of disease-related causes. Of the 41 total cases, 10

Table 1 Survival Based on World Health Organization Classification of Dogs Diagnosed With Splenic Lymphoma (n = 28)

World Health Organization Classification	IHC Cell Origin	Number of Dogs	Day (Range)		Median Survival (Days)	1 Year (%)
			Overall Survival	Disease-Free Interval		
Marginal zone lymphoma	B cell	11	377 (0–1,257)	377 (0–1,257)	NR	63.6
Mantle cell lymphoma		9	502 (357–1,300)	502 (235–1,300)	NR	88.9
Other B cell lymphoma		3	561 (191–714)	561 (149–714)	561	50.0
Null cell/NK cell	Non-B/non-T cell	2	8 (0–16)	0	0	0.0
Peripheral T cell lymphoma	T cell	3	4 (2–17)	0	4	0.0

IHC, immunohistochemical; NR, not reached; NK, natural killer.

dogs died or were euthanatized because of other causes including congestive heart failure, diabetes, chronic kidney failure, other cancers, road traffic accident, and development of multiple subcutaneous abscesses followed by septic shock.

In 9 cases, second opinion histopathology could not be performed because the slides had been discarded and were, therefore, unavailable, the diagnostic laboratory would not release them, or because of international shipping restrictions. In 4 remaining cases, second opinion histopathology reclassified submitted tissue as non-lymphoma, excluding the case from further survival analysis. Twenty-eight cases were classified based on the WHO classification of canine malignant lymphoma and further survival analysis was performed (Table 1).⁵ One of the 28 cases was reclassified to another immunophenotype (T cell lymphoma reclassified to non-B/non-T cell lymphoma) by the study pathologist (TS). Nineteen cases were censored for survival including 2 that died on the day of splenectomy. Comparing a survival between the 41 first opinion histopathology group and the 28 cases that also had second opinion histopathology performed, no significant difference in survival ($P=.759$) or DFI was observed ($P=.711$).

Overall, 1-year mean (\pm SD) survival rate for canine splenic lymphoma (n = 28) was $59.8 \pm 18.8\%$ (Fig 1). Median survival times were not reached, with a median follow-up time of 367 days (range 0–1,300 days). The 1-year mean survival rate for splenic B cell lymphoma (n = 23) was $69.8 \pm 9.6\%$, median survival times were not reached, with a median follow-up of 457 days (range 120–1,300 days). The 1-year mean survival rate for splenic T cell lymphoma (n = 3) was 0%, with a mean survival time of 5.7 ± 3.8 days (range 2–17 days) with a median of 2 ± 2 days. Two cases that were diagnosed with non-B/non-T cell lymphoma had a survival time of 0 and 16 days postoperatively.

Cases diagnosed with MZL (n = 11) had a 1-year survival rate of $63.6 \pm 14.5\%$, with a median follow-up of 220.5 days (range 120–1,257 days). Median survival times were not reached. Cases diagnosed with MCL (n = 9) had a 1-year survival rate of $88.9 \pm 10.5\%$, with a median follow-up of 502 days (range 357–1,300 days). Median survival times were not reached. There was no significant difference in survival between cases diagnosed with MZL and MCL ($P=.135$; Fig 2). MCL and MZL (n = 20) were the most common forms of splenic lymphoma in our study and had a 1-year survival

rate of 75%, with a median follow-up time of 428 days (range 120–1,300 days) and median survival not yet reached (Table 1).

Of the prognostic factors evaluated, age ($P=.769$), sex ($P=.14$), weight ($P=.082$), breed (no predominant breed), preoperative thrombocytopenia (n = 5; $P=.329$), preoperative anemia (n = 17; $P=.065$), and the presence or absence of perioperative DIC (n = 6; $P=.505$) were not of prognostic significance. The addition of adjuvant chemotherapy ($P=.827$) either pre- or postoperatively did not provide a survival benefit (Fig 3). Protocols used in 15 dogs receiving chemotherapy varied (Table 2). Diagnosis of splenic lymphoma as an incidental finding (n = 12) also did not provide a survival advantage (DFI; $P=.213$ and median survival time; $P=.301$). Dogs that presented with clinical signs had a shorter median DFI (149 days; range 0–1,300; $P=.006$) and a significantly shorter median survival time (222 days; range 0–1,300; $P=.011$) compared to dogs that did not present with clinical signs (n = 14). Hemoabdomen caused by splenic rupture was seen in 9/41 cases of which, 4 cases did not have 2nd opinion histopathology performed because of logistical issues and 2 cases were confirmed not to be lymphoma on 2nd

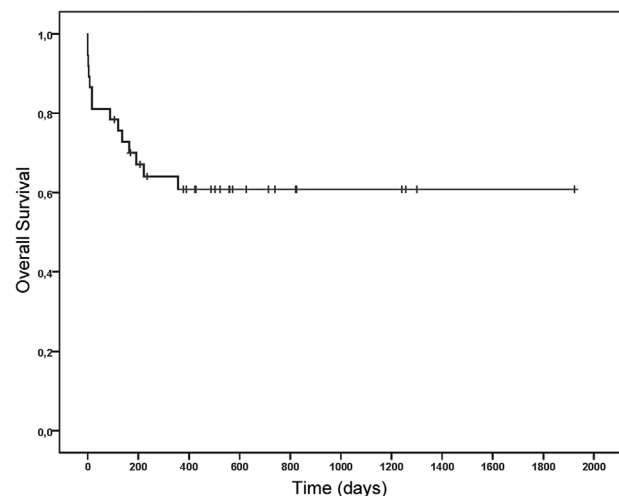


Figure 1 Survival analysis for canine splenic lymphoma (28 dogs). The overall 1-year survival rate was 59.8%.

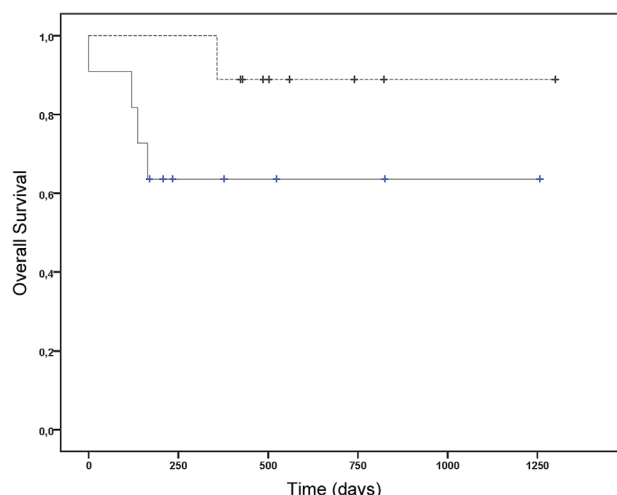


Figure 2 Survival analysis for canine splenic marginal zone lymphoma (solid line) versus mantle cell lymphoma (dotted line).

opinion histopathology. One case died the day of splenectomy because of anesthetic complications. In the 3 cases in which splenic lymphoma was confirmed by 2nd opinion histopathology, hemoabdomen was a significant negative prognostic factor for median DFI (71 days; range 0–234; $P=.025$) and median survival (120 days; range 0–234; $P=.026$). All hemoabdomen cases were identified as MZL with disease was confined to the spleen ($n=2$) or hepatosplenic (1).

Evidence of disease at additional sites ($n=7$) was found to be a significant negative prognostic factor compared to disease confined to the spleen alone ($n=21$). Dogs with disease of the spleen alone had a 1-year survival rate of

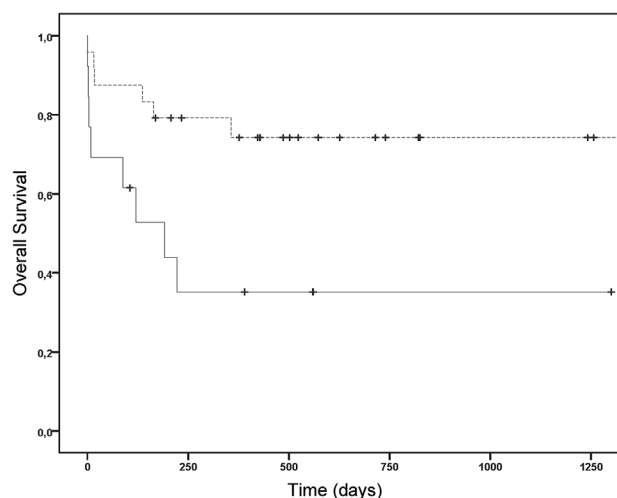


Figure 3 Survival analysis for disease distribution. Splenic lymphoma confined to the spleen (dotted line) has a significantly better outcome compared to dogs with lymph nodes and other organ involvement (solid line).

$74.2 \pm 9.1\%$ and a median follow-up time of 486 days (range 16–1,300 days; $P>.001$). Disease involving the peripheral lymph nodes and intestines ($n=2$) was a poor prognostic indicator ($P=.014$) with survival rates of 4 and 428 days (Fig 4). Hepatosplenic lymphoma ($n=4$) carried the worst prognosis ($P>.001$) with a 0% 1-year survival rate (range of survival; 2–559 days), with a median survival time of 155 days. Three of 4 hepatosplenic cases were immunohistochemically classified as B cell lymphoma (MZL, MCL, and a diffuse B cell lymphoma) and 1 was classified as a T cell lymphoma, which also had involvement of the intestines and local lymph nodes.

DISCUSSION

The overall 1-year survival of canine splenic lymphoma in our study was 59.8%, which is comparable to the previously reported 1-year survival range of 14–51% for canine multicentric lymphoma.^{12–16} There was a wide range in overall survival in our study (0–1,300 days). However, division of cases according to the extent of disease, immunohistochemical cell origin, or histological subtype according to the WHO classification for canine lymphoma proved useful in drawing several conclusions regarding outcome, including a significant better outcome in cases with disease confined to the spleen, a B cell phenotype, and histological WHO subclasses MZL and MCL. A poorer outcome can be expected when disease is widespread, with liver involvement and off T cell origin.

One of the most striking results of our study was that primary splenic lymphoma, defined as lymphoma confined to the spleen, had a good survival outcome. This supports the possibility of long-term control of disease or even cure by splenectomy alone, as was suggested by earlier studies.^{4,5,7} The long-term favorable outcome of splenic lymphoma treated with splenectomy may be because of the indolent nature of primary splenic lymphoma. The question that remains is whether or not adjunctive chemotherapy should play a role in the treatment of canine splenic lymphoma. In our study, the addition of chemotherapy did not improve survival; however, the multi-institutional nature of our study makes it difficult to interpret this finding. It is possible that chemotherapy was more likely to be recommended in cases with a worse prognosis, creating selection bias. Also, there was a great variability in the types of chemotherapy courses given and a relatively small number of cases that received chemotherapy, so it is possible that a type II error exists.

Based on our study, survival was negatively impacted if lymphoma was identified in locations aside from the spleen. It is, therefore, important to stage cases preoperatively and intraoperatively, taking samples of enlarged lymph nodes, liver and, if indicated, intestines or other organs. Cases with extension of lymphoma beyond the spleen may benefit from chemotherapy^{17–19}; however, splenic lymphoma confined to the spleen may be managed successfully with splenectomy and monitoring alone. According to WHO lymphoma stage

Table 2 Outcomes for Dogs Receiving Splenectomy and Adjunctive Chemotherapy

Chemotherapy Protocol	World Health Organization Classification	Location	Survival (Days)
Chlorambucil/prednisone	Marginal zone lymphoma	Spleen	169
Doxorubicine			207
Chlorambucil/prednisone			825
CHOP	Mantle cell lymphoma	Spleen	136
Chlorambucil/prednisone			164
CHOP			822
Doxorubicine			740
Chlorambucil/prednisone			502
CHOP			357
CHOP	Peripheral T cell lymphoma	Spleen, liver	423
Prednisone			559
Vincristine/cyclophosphamide			2
Chlorambucil/prednisone	Follicular lymphoma	Spleen, lymph nodes	561
Chlorambucil prednisone			714
CLOP	Large B cell lymphoma	Spleen, liver	191

CHOP, vincristine, doxorubicine, cyclophosphamide, and prednisone; CLOP, vincristine, cyclophosphamide, L-asparaginase, and prednisone.

classification, splenic involvement is classified as stage IV.^{12,13,15,20–22} Based on our findings, this classification seems to be a misnomer in cases of primary splenic lymphoma, as the disease appears to take a more indolent course than other stage IV tumors.^{2,4,5}

Another important finding in our study is that there was a significant difference in survival between the 6 WHO canine lymphoma subtypes identified. The prognosis for T cell lymphoma was poor compared to B cell lymphoma.^{16,23,24} In our study, all cases of canine splenic T cell lymphoma died perioperatively and the median survival time was 2 ± 2 days, whereas median survival times for B cell lymphomas were not reached, as most cases were either still alive at the end of the accrual period or died of other causes. The 1-year survival for canine splenic lymphoma of B cell origin in our study was

69.8%. Publications reporting survival for other forms of canine lymphoma (e.g., canine multicentric lymphoma) are numerous; however, multicentric lymphoma represents widespread disease, whereas primary canine splenic lymphoma is a localized form of lymphoma and may even have an indolent nature. It is to be expected, from a cancer biology point of view, that survival for dogs with localized disease will be significantly longer when compared to patients suffering from a disseminated form of cancer.

The overall favorable prognosis of the canine splenic B cell lymphomas in our study was likely because of the large proportion of MZL and MCL. These 2 predominant splenic lymphoma subtypes may have an indolent course of disease.^{1,4,5,25} MZL has been associated with long survival periods in previous studies in dogs.^{4,5} Splenic MCL has not previously been reported in dogs. Human splenic MZL is associated with an indolent course of disease in which splenectomy alone may be curative.^{7–10} In contrast, human splenic MCL is associated with an overall poor outcome,^{26–30} although there are a few reports on more indolent cases.^{29–31} The difference between the more indolent splenic canine MCL and the poor prognosis for its human counterpart illustrates an important consideration between the species. Although the WHO histopathological classification for human lymphoma can be applied to canine lymphoma cases in the form of the WHO canine lymphoma classification on a histopathological basis, the prognosis by subtype may differ between species. As there are significant differences in survival between subtypes in our study, the WHO classification for canine lymphoma may prove to be useful in determining the prognosis for dogs with lymphoma.

Of the prognostic factors analyzed, patients with clinical signs, such as lethargy, weight loss, abdominal distension, or abdominal pain at the time of diagnosis, had a significantly poorer outcome. The reason for this may be that the lymphoma in these cases was more likely to be of T cell origin (i.e., peripheral T cell lymphoma), hepatosplenic

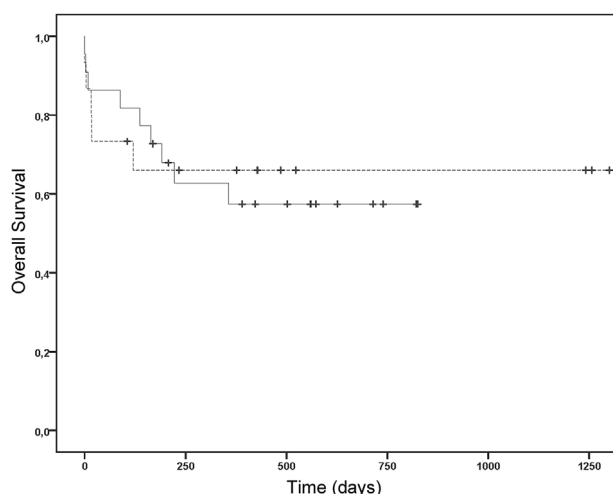


Figure 4 Survival analysis for splenectomy versus splenectomy with adjuvant chemotherapy (dotted line) with adjuvant chemotherapy (solid line). The addition of chemotherapy was not of additional value for survival.

origin, or have multiple organ involvement, creating a poorer prognosis overall. This is consistent with other studies on canine T cell lymphoma^{18,39,40} and lymphoma in general.^{13,16,22,24} These results support our hypothesis that the extent of disease and WHO canine lymphoma classification can be used to prognosticate disease outcome. The presence of clinical signs at the time of diagnosis is reported to be a prognostic indicator and was a significant predictor for survival in our study.^{32,33}

Hemoabdomen was diagnosed in cases with lymphoma confined to the spleen as well as cases with liver involvement. These cases were all classified as MZL. Studies on other forms of splenic malignancies³⁴ and spontaneous hemoperitoneum^{35–37} have reported that hemoabdomen at presentation has a negative effect on disease outcome.^{34–37} Though the small number of cases and rather wide standard deviation show how much variation there is in survival, hemoabdomen was associated with a poor prognosis in canine splenic lymphoma in our study, with a median survival time of 120 days.

In previous studies, canine hepatosplenic lymphoma has been associated with T cell lymphoma, resulting in a poor overall outcome.^{18,19} Of the 4 cases of hepatosplenic lymphoma in our study, only 1 was classified as a T cell lymphoma. The other 3 were a variety of B cell lymphomas (MZL, MCL, and follicular lymphoma). This diverse group also showed a wide range of survival times and might explain the slightly better outcome for median survival time of 155 days in our study compared to the previously reported overall survival of <1 month after diagnosis in cases of hepatosplenic lymphoma.^{18,19} Hepatosplenic lymphoma has a poor prognosis compared to cases in which lymphoma was confined to the spleen.

No hematological parameters, including DIC, thrombocytopenia, and anemia, were of prognostic value in our study. Perioperative DIC,³⁸ thrombocytopenia,^{5,12} and anemia^{5,34,41,42} have been suggested to be of prognostic value in previous studies on canine splenic and multicentric lymphoma, as well as a study assessing prognostic factors in canine splenic masses.^{34–37} Of the other prognostic factors analyzed, demographic categorical data showed little prognostic value. No breed predisposition was found in our study, which is consistent with previous reports on canine lymphoma.^{2,5,12} There was no sex predisposition noted, and both age and weight ranged widely. In people, there is a predisposition to males for both Hodgkin's lymphoma and non-Hodgkin's lymphoma,⁴³ which has also been reported for canine multicentric lymphoma.^{33,44}

If disease is confined to the spleen, surgical treatment alone may be sufficient in cases of primary splenic lymphoma, with close monitoring of the patient for recurrence at other sites. Chemotherapy did not improve survival time in these cases in our study. WHO classification had prognostic significance in our evaluation of canine splenic lymphoma. When lymphoma extends beyond the spleen, a more classical approach to lymphoma treatment may be indicated. The benefit of splenectomy in these cases is not known and further research is warranted.

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DISCLOSURE

The authors declare no conflicts of interest related to this report.

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