Premature death in dogs with nontraumatic hemoabdomen and splenectomy with benign histopathologic findings

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OBJECTIVE
To determine whether premature death occurred among dogs with nonmalignant splenic histopathologic findings after splenectomy for nontraumatic hemoabdomen.

ANIMALS
197 dogs with nontraumatic hemoabdomen that underwent splenectomy and histopathologic evaluation between 2005 and 2018.

PROCEDURES
Information was obtained from electronic medical records, dog owners, and referring veterinarians to determine patient characteristics, histopathologic findings, survival information, and cause of death. Dogs were grouped based on histopathological diagnosis and outcome, and median survival times (MSTs) and risk factors for death were determined.

RESULTS
Histopathologic findings indicated malignancy in 144 of the 197 (73.1%) dogs with nontraumatic hemoabdomen. Hemangiosarcoma was diagnosed in 126 dogs (87.5% of those with malignancies and 64.0% of all dogs). Nine of 53 (17%) dogs with nonmalignant histopathologic findings had an adverse outcome and premature death, with an MST of 49 days. Risk factors for this outcome included low plasma total solids concentration, an elevated hemangiosarcoma likelihood prediction score, and a medium or high hemangiosarcoma likelihood prediction score category.

CONCLUSIONS AND CLINICAL RELEVANCE
This study showed that there is a group of dogs with nontraumatic hemoabdomen due to splenic disease that have nonmalignant histopathologic findings after splenectomy, but nonetheless suffer an adverse outcome and die prematurely of a suspected malignancy. Further evaluation of potential at-risk populations may yield detection of otherwise overlooked malignancies.
A recent retrospective study examined the cause of death and survival time in dogs with splenic hematomas and identified an 11% (4/35) rate of adverse outcomes. Dogs with adverse outcomes had survival times well below the overall MST, and they had suspicious or documented outcomes related to hemangiosarcoma or other malignancies. Unexplained or unexpected early death is a clinically relevant finding in this population, but there is a paucity of sufficiently large studies to support these findings.

The objective of the present study was to determine whether premature death occurred in a population of dogs with nonmalignant histopathologic findings following splenectomy for nontraumatic hemoabdomen. The second objective was to identify premortem factors that may help predict which dogs in this population might have adverse outcomes. We hypothesized that some dogs with nonmalignant histopathologic findings would have adverse outcomes that resulted in premature death. We anticipated that the findings could assist emergency clinicians, surgeons, and owners in determining the prognosis for dogs treated for nontraumatic hemoabdomen due to splenic disease.

Materials and Methods

Animals

The electronic medical records at our veterinary teaching hospital were searched to identify dogs that incurred a charge for a splenectomy between January 2005 and December 2018. This query yielded 701 dogs, the records for which were then reviewed to determine eligibility for the study. To be included in the study, dogs were required to have had a splenic mass or nodule and peritoneal blood documented at or near the time of splenectomy. Dogs were excluded if they had concurrent GDV, septic or bile peritonitis, splenic torsion, splenic abscess, insufficient records, no histopathologic data, or a lack of follow-up data.

Data collection

Medical records were reviewed to determine the dogs’ sex, neuter status, breed, age, and weight at presentation. Additional data were collected regarding first platelet count, first plasma total solids concentration (as measured by refractometer), and whether a blood transfusion was administered during hospitalization. The estimated peritoneal blood volume (if recorded) and the presence of a mass or nodule were recorded for the spleen, liver, mesentery (including omental and mesenteric lymph nodes), and other abdominal structures. Any imaging results within 2 weeks of presentation were recorded. The presence or absence of pleural effusion, pericardial effusion, cardiac mass or nodule, and pulmonary pattern was recorded. Abdominal ultrasound results were included only if performed or interpreted by a diplomate of the American College of Veterinary Radiology. Echocardiography results were only included if performed or interpreted by a diplomate of the American College of Veterinary Internal Medicine in Cardiology. Point-of-care ultrasound results were included when interpreting the presence or absence of pericardial effusion or pleural effusion.

For abdominal ultrasonography, the presence or absence of a splenic mass or nodule, hepatic mass or nodule, or other abdominal mass or nodule was recorded. Platelet count, plasma total solids concentration, thoracic radiograph findings, and weight were used to calculate a hemangiosarcoma likelihood prediction (HeLP) score. This scoring system (0 to 100) classifies dogs as being at a low (0 to 40), medium (41 to 55), or high (> 55) risk for hemangiosarcoma when nontraumatic hemoabdomen is present.

The histopathologic results were recorded as hemangiosarcoma, other malignancy, benign lesion, or normal for each site. At the time of the study, it was standard practice at our hospital for the entire spleen to be submitted for histopathologic evaluation, often with several slices obtained for analysis. All such tissues were interpreted by a diplomate of the American College of Veterinary Pathologists at our institution. Based on imaging, surgery, and histopathologic findings at the time, dogs were assessed to have metastatic disease or no metastatic disease. Documentation of the same malignancy in 2 locations was considered to be metastasis.

Survival time was defined as the time in days from surgery until confirmed date of death or by owner verification as being currently alive. At least 14 months elapsed between the end of the study period and collection of survival data.

If any of the aforementioned information was not found in the medical records, the owner, referring veterinarian, or primary veterinarian was contacted by phone, email, or mail to complete data collection.

Statistical analysis

Prior to survival time evaluation, outcome was classified as death related to malignancy or death unrelated to malignancy. This classification was based on clinical signs at the time of death and necropsy results. Signs of death related to malignancy included death from hemorrhage, hemorrhagic effusion, anemia, systemic inflammatory response syndrome, disseminated intravascular coagulopathy, pulmonary metastatic disease, sudden collapse, and sudden death. Signs of death unrelated to malignancy included death from sepsis or infection, thromboembolism, arrhythmia, direct surgical complication, unrelated malignancy, or any other unrelated fatal condition. In the uncommon event that clinical signs at the time of death were unclear, death was presumed to be related to malignancy. Dogs with nonmalignant histopathologic findings that died of a condition related to malignancy were considered to
have died prematurely. Dogs with death unrelated to malignancy were censored during survival analysis.

Prior to data analysis, dogs were sorted into 4 groups: nonmalignant histopathologic findings and death unrelated to malignancy as described above (expected death), malignant histopathologic findings and death related to malignancy (expected death), nonmalignant histopathologic findings and premature death as explained previously (unexpected death), and malignant histopathologic findings and death unrelated to malignancy (unexpected death, but not adverse).

All statistical analyses were performed using statistical software (JMP, version 15.0.0, SAS Institute Inc.). All numeric variables were assessed for normality using the Anderson-Darling normality test. Normally distributed data are presented as mean ± SD. Nonnormally distributed data are presented as a median (range).

Survival analysis was performed using Kaplan-Meier analysis and log-rank tests. All variables were assessed for associations with death over the follow-up period (with hazard ratios interpreted as relative risk) by bivariable (only 1 independent variable) and then multivariable Cox proportional hazards analysis. Since an objective of the study was to assess the risk of death using variables available before histopathologic evaluation, variables that directly referenced histopathologic findings were excluded from multivariable Cox proportional hazards analysis. These excluded variables consisted of histopathologic findings for each organ, presence or number of malignancies, metastasis conclusions, survival to discharge, whether a necropsy was performed, and variables for which the model did not converge. For analysis of dogs with nonmalignant histopathologic findings, only bivariable analysis was performed because of the small number of dogs. Values of P < 0.05 were considered significant for all tests.

Results

A total of 197 dogs were included in the study. Other dogs were excluded for having a splenic mass or nodule without hemoabdomen (n = 366), concurrent GDV (34), concurrent septic or bile peritonitis (20), splenic torsion (19), lack of histopathologic data (8), concurrent trauma (7), thrombus or infarction without a mass or nodule (6), insufficient records (6), and splenic abscess (5). Five other dogs were excluded due to splenectomy for diaphragmatic hernia, intestinal entrapment, bilobed spleen, splenomegaly, and immune-mediated disease (1 each). Thirty dogs were excluded because of lack of follow-up data.

Descriptive data for included dogs were summarized (Supplementary Table S1). Overall, 104 (52.8%) dogs were male and 93 (47.2%) were female. Median age of all dogs was 10.8 years (range, 2.5 to 15.4 years), and mean ± SD body weight was 30.5 ± 11.5 kg.

Based on the histopathologic diagnosis, 144 of 197 (73.1%) dogs had a malignancy. In total, 126 dogs (87.5% of dogs with malignancies; 64.0% of all dogs) had hemangiosarcoma, 3 of which had hemangiosarcoma of the spleen with a second unique malignancy. Another 17 dogs had a nonhemangiosarcoma malignancy in the spleen, 2 of which had a second unique malignancy. The remaining 54 dogs had a benign lesion in the spleen, but 1 of those dogs also had a cecal gastrointestinal tumor.

There were 44 dogs with nonmalignant histopathologic findings and death unrelated to malignancy, 123 dogs with malignant histopathologic findings and death related to malignancy (expected death), 9 dogs with nonmalignant histopathologic findings and premature death (ie, unexpected death due to a condition related to malignancy), and 21 dogs with malignant histopathologic findings and death unrelated to malignancy.

Most dogs (121/197 [61.4%]) received a blood transfusion. Approximately half (97/197 [49.2%]) were categorized as having a low HeLP score. Very few dogs (5/189 [2.6%]) had metastasis evident on thoracic radiographs. The overall rate of survival to discharge was 86.8% (171/197).

To highlight the difference between histopathologic diagnosis and outcome, characteristics of the 9 dogs with nonmalignant histopathologic findings and adverse outcomes were summarized (Supplementary Table S2). These 9 dogs represented 17% (9/53) of dogs with nonmalignant histopathologic findings after splenectomy. Three of the 9 dogs died of hemorrhagic pericardial effusion, 3 died of hemoabdomen and bleeding, and 3 died of systemic inflammatory response syndrome or multiorgan dysfunction syndrome, disseminated intravascular coagulopathy, or sudden collapse and death. For 1 dog, the owner reported that a necropsy was performed by a veterinarian, indicating a gross diagnosis of metastatic hemangiosarcoma. However, the necropsy report was unavailable for review. Five of the dogs underwent abdominal ultrasonography, and 8 underwent thoracic radiography. For 6 dogs with thoracic radiographs, findings were normal, whereas 1 other dog had a potential nodule that was assessed by a radiologist to be a positioning artifact. This dog was later diagnosed with a right atrioventricular groove mass and pericardial effusion 2.5 months after surgery.

The MST for the 44 dogs with nonmalignant histopathologic findings and death unrelated to malignancy was 628 days (range, 1 to 2,566 days), 43 days for the 123 dogs with malignant histopathologic findings and death related to malignancy (range, 0 to 952 days), 49 days for the 9 dogs with nonmalignant histopathologic findings and premature death (range, 0 to 669 days), and 656 days for the 21 dogs with malignant histopathologic findings and death unrelated to malignancy (range, 0 to 2,408 days). Survival time was significantly (P < 0.001) lower for dogs with malignant versus nonmalignant histopathologic
findings but not significantly (P = 0.11) different between dogs with malignant histopathologic findings and death related to malignancy and those with nonmalignant histopathologic findings and adverse outcomes (Figure 2).

Results of multivariable Cox proportional hazards analysis were summarized to identify factors associated with death over the study follow-up period among all included dogs (Table 1). Higher amount of abdominal blood (mL/kg) and lower platelet count were associated with an increased risk of death. In addition, failure to perform imaging and the presence of a hepatic mass or nodule were also associated with an increased risk of death. Among dogs with nonmalignant histopathologic findings only, the risk of death decreased with low-category HeLP scores (ie, 0 to 40; relative risk, 0.261; 95% CI, 0.070 to 0.976; P = 0.046) or with increasing plasma total solids concentrations (relative risk, 0.531; 95% CI, 0.281 to 0.997; P = 0.049) but increased with increasing HeLP score (relative risk, 1.060; 95% CI, 1.015 to 1.113; P = 0.011).

Discussion
As hypothesized, this study identified a group of dogs (9/53 [17%]) with nonmalignant histopathologic findings that suffered premature death at a clinically significant rate similar to or greater than previously reported (4/35 [11%]). The 4 dogs with adverse outcomes in the previous study had survival times ranging from 138 to 522 days after splenectomy of a histopathologic hematoma, compared with an overall MST of 647 days for all dogs with splenic hematomas. The 9 dogs in the present study that died prematurely had hemorrhagic effusion of the pericardium or peritoneum. Potential explanations for these findings could include misdiagnosis due to inherent histopathologic diagnostic difficulty, misdiagnosis due to insufficient histopathologic samples.
simultaneous undetected malignancy, or postoperative novel malignancy formation. Undetected malignancy would be expected to have a survival time similar to that of stage II hemangiosarcoma with splenectomy alone (19 to 86 days).\(^2,5,9\) In fact, the group with nonmalignant histopathologic findings that suffered adverse outcomes had an MST of 49 days.

The present study identified several risk factors for death related to malignancy and adverse outcomes. The multivariable analysis showed that the risk of death increased with increasing volume of abdominal blood (mL/kg), decreasing platelet count, lack of imaging performed, and the finding of a hepatic mass or nodule at surgery. The finding of a hepatic mass or nodule in surgery as a risk factor is notable. This suggests that the dogs may have died of metastatic hemangiosarcoma or another malignancy that was either missed or not sampled at surgery. On bivariable analysis, risk factors for death among dogs with nonmalignant histopathologic findings and premature death included medium- or high-category (vs low-category) HeLP scores, increasing HeLP score, and low plasma total solids concentration.

Considering that many of the risk factors this study identified were associated with hemorrhage, hemorrhage may obfuscate the diagnosis of histopathologic malignancy of a ruptured splenic mass. For example, 1 dog with carcinoid liver histopathologic findings was later found to have hemangiosarcoma in the liver. The study supported the use of a preoperative CBC and thoracic radiographs in this population. Schick et al\(^6\) developed a scoring system, the HeLP score system based on body weight, plasma total solids concentration, platelet count, and radiographic lung patterns, to assess for low, medium, or high risk of hemangiosarcoma among dogs with nontraumatic hemoabdomen. Our findings support the use of the HeLP score categories to assess the risk of not only hemangiosarcoma but also malignancy in general for this population. The findings also support thorough abdominal exploration, multiple organ tissue sampling, histopathologic evaluation of several areas of the spleen, and submission of the entire splenic tissue for histopathologic evaluation.

The survival to discharge rate in the present study was 86.8%, but was likely lower because 8 dogs were excluded due to lack of histopathologic findings. These 8 dogs underwent splenectomy but died or were euthanized near the time of surgery, typically due to presumed metastatic nodules. Two of those 8 dogs had necropsies that revealed metastatic hemangiosarcoma.

Despite the above findings, the present study had several limitations. Most of the dogs of interest that suffered premature death despite nonmalignant histopathologic findings did not undergo necropsy. Although, in the authors’ experience, hemorrhagic pericardial and peritoneal effusions are likely neoplastic in older dogs, other causes cannot be ruled out. Due to the retrospective nature of the study, it was difficult to completely blind the process of identifying the cause of death from the histopathologic diagnosis. This constituted an important source of potential bias in the study. Many dogs had sudden collapse with pale gums but no definitive diagnosis at time of death. The lack of further diagnostic tests or necropsy may have been due to the attending veterinarian’s confidence in the clinical diagnosis or resistance to pursue further diagnostic tests for a dog that has already undergone histopathologic evaluation, which is the gold standard diagnostic test. Likewise, owner recollection of events and signs at the time of death could be expected to be imperfect over the course of such an extended study. The cause of death assessment was exhaustive among all resources (study hospital records, referring veterinarian records, and owner contact via several methods), but such data can be limited.

Considering the potential for serious adverse outcome, dogs with nontraumatic hemoabdomen from splenic disease, nonmalignant histopathologic findings, and the identified risk factors may benefit from postoperative screening. Such screening could include echocardiography, abdominal ultrasonography, thoracic radiography, or tissue sampling or aspirates. Future studies could actively screen dogs with the listed risk factors over time to determine the likelihood of finding causes of an otherwise unexpected outcome. Screening may include imaging to identify a right atrial mass, hemopericardium, abdominal mass or nodule, or hemoabdomen. Overall, the present study found that there is the potential for premature death in dogs with nonmalignant histopathologic findings after splenectomy for hemoabdomen.

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**Supplementary Materials**

Supplementary materials are posted online at the journal website: avmajournals.avma.org