Clinical factors associated with death before discharge and overall survival time in dogs with generalized megaesophagus

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**Objective**—To investigate the association of 6 clinical features with outcome of dogs with generalized megaesophagus.

**Design**—Retrospective cohort study.

**Animals**—71 client-owned dogs with radiographic evidence of generalized esophageal dilation.

**Procedures**—Medical records were reviewed for data on signalment, age at onset of clinical signs, body weight, evidence of undernutrition, and the administration of drugs to treat or prevent esophagitis. Radiographs were reviewed for evidence of aspiration pneumonia (AP) and to calculate the relative esophageal diameter. Details of outcome were collected from the medical records and by contacting owners and referring veterinarians. The association of 6 factors with death before discharge and overall survival time was assessed.

**Results**—Overall median survival time was 90 days. Nineteen (26.7%) patients died before discharge from the hospital. Radiographic evidence of AP was both positively associated with death before discharge and negatively associated with overall survival time. An age at onset of clinical signs of >13 months was negatively associated with overall survival time. No evidence of an association of the degree of esophageal dilation or the use of drugs to prevent or treat esophagitis with death before discharge or overall survival time was found.

**Conclusions and Clinical Relevance**—Radiographic evidence of AP and the age at onset of clinical signs were the only variables found to be significantly associated with survival time in this study, and this should be considered when advising on prognosis in dogs with megaesophagus. (J Am Vet Med Assoc 2011;238:1622–1628)

Esophageal dilation may be caused by structural or functional diseases of the esophagus and may be localized or diffuse. Structural diseases causing esophageal dilation may include vascular ring anomalies, foreign bodies, strictures, extraesophageal or intraesophageal masses, and hiatal hernias. These diseases tend to cause esophageal obstruction with localized dilation of the esophagus proximal to the obstruction. In contrast, functional diseases, which result in decreased or absent esophageal motility, tend to result in a diffuse dilation that is referred to as ME. On the basis of when clinical signs occur, cases of ME are often categorized as being either congenital or acquired, although the distinction between these is inconsistent in the literature. Whereas congenital ME is considered to be idiopathic, acquired ME may be primary (idiopathic) or secondary to other diseases. A number of diseases in dogs, such as myasthenia gravis, hypoadrenocorticism, canine dystautonomia, tetanus, polyradiculoneuritis, leiomyoma, and possibly hypothyroidism, have been suggested to be etiologically associated with ME.

Megaesophagus is diagnosed by the identification of esophageal dilation on survey or contrast radiographs. Thoracic radiography may also allow the diagnosis of structural diseases causing esophageal dilation (e.g., esophageal masses and foreign bodies). Megaeosophagous can result in artifactual esophageal dilation during anesthesia. Sedation has been shown to have a mild effect on esophageal motility in manometric studies, and it is recommended that the radiographic diagnosis of ME be made without chemical restraint. Anecdotally, β2-adrenoceptor agonists have been reported to have a marked effect on esophageal function. However, published evidence that gross esophageal dilation can develop in a normal dog following sedation is lacking.

Megaesophagus commonly results in regurgitation. Unlike vomiting, regurgitation is not a reflex event;
therefore, concurrent laryngeal closure does not occur. Regurgitating patients are thus at a high risk of developing AP. In people, the diagnosis is made on the basis of the presence of respiratory tract signs and radiographic evidence of a newly developed pulmonary infiltrate in a patient known to be at risk.\(^\text{18}\) In dogs, AP is most often characterized radiographically by an alveolar pattern or lobar consolidation in the dependent areas of the lung, although interstitial patterns have also been described.\(^\text{19,20}\) Aspiration pneumonia has been reported to be the most common cause of death in dogs with ME,\(^\text{2,21}\) Alternatively, dogs with intractable esophageal disease may become malnourished, resulting in severe weight loss and emaciation,\(^\text{21,22}\) or have uncontrollable regurgitation and therefore become socially problematic.\(^\text{21}\)

In some dogs, especially those with secondary ME in which the underlying cause is successfully treated, esophageal function may improve.\(^\text{2,4,14,15,23}\) Spontaneous improvement in patients with both the congenital\(^\text{24,25}\) and idiopathic acquired\(^\text{2}\) forms of the disease has also been reported. In congenital cases, improvement may be the result of esophageal maturation, which can occur up to 1 year of age.\(^\text{25,26}\) It is possible that improvement in esophageal function improves the prognosis in these dogs.

Despite these reports, current published knowledge\(^\text{12,27-30}\) suggests that ME in dogs is a disease with a guarded to poor prognosis, particularly in patients in which no underlying cause is found. This widely held belief appears to be based on a single study of 79 dogs with generalized ME by Harvey et al.,\(^\text{21}\) in which almost 40% of the dogs were treated surgically with cardiomyotomy, a procedure now considered to be inappropriate for this condition.\(^\text{1}\) In that study,\(^\text{21}\) survival ranged from 0 to 90 months (13 dogs alive at the time the study was published), with an MST in nonsurgically treated dogs of 1 month.

Other reports have suggested that the prognosis is better if the underlying cause can be treated,\(^\text{1,28}\) if the animal responds to dietary management,\(^\text{29}\) and if the diagnosis is made early in the disease process.\(^\text{1}\) Additionally, Tams\(^\text{31}\) suggests that in congenital cases, the greater the degree of esophageal dilation, the worse the prognosis. Overall, there is little in the peer-reviewed literature to suggest which factors affect survival.

The objectives of the study reported here were to estimate the MST of dogs with generalized ME, to investigate the association between 6 possible risk factors and death before discharge from the hospital, and to investigate the association of these risk factors with overall survival time in these dogs.

### Materials and Methods

**Case selection**—Dogs with ME were identified by a search of the University of Glasgow Small Animal Hospital radiologic and clinical databases for all dogs that underwent radiography between January 1996 and October 2007. Search terms included megaesophagus, oesophagus, and oesophageal dilation as radiographic diagnoses. Complete medical records and at least 1 lateral thoracic radiograph of diagnostic quality had to be available for inclusion of the patient in the study. Radiographs had to have evidence of generalized esophageal dilation on the lateral thoracic view. Patients without clinical signs of vomiting or regurgitation (these were difficult to distinguish from the information in medical records) were included if they had persistent generalized esophageal dilation visualized on serial radiographs over a minimum of 2 weeks or evidence of gross esophageal dilation at necropsy, to ensure esophageal dilation was not a transient inconsequential finding.

Patients for which the only radiographs having ME were those taken under general anesthesia or taken when animals were sedated with α-adrenoceptor agonists were excluded, as esophageal dilation could have been artifactual in these animals. Cases in which dogs were sedated with acepromazine and opioids were included because of absence of evidence that these drugs cause gross esophageal dilation and the risk of introducing bias by excluding less debilitated patients, which are those likely to be administered sedatives.

**Data collection**—Factors considered as being of interest were recorded wherever possible from the medical records from the first visit to the hospital. These factors included the date of first examination, signalment (including age at diagnosis), age at the onset of clinical signs, body weight, whether or not there was evidence of undernutrition (either the owner describing recent weight loss or the clinician describing the patient as underweight, thin, or having a body condition score < 3/9), and the presence or absence of vomiting or regurgitation. All drugs administered during hospitalization and at discharge (including sedatives administered for radiography) were also recorded. The final diagnoses, as made by the attending clinician, were also recorded with particular emphasis on the identity of diseases thought to be etiologically associated with ME.

All radiographs were examined and reported by a board-certified radiologist when they were obtained. Radiographs and contemporaneous reports were reviewed for the present study by 2 of the authors (ARM and RB) who had no knowledge of the patients’ outcome. Radiographs were assessed and measurements were made independent of evaluation of the medical records. The earliest lateral thoracic radiograph with subjective evidence of esophageal dilation without aboral esophageal obstruction, and fulfilling the criteria noted regarding chemical restraint, was used for data collection. The date of radiography and any sedatives administered were recorded. The RED was calculated from the maximal esophageal diameter and the thoracic inlet diameter (both measured in millimeters) as described by Wray and Sparkes.\(^\text{3}\) Evidence of AP and other thoracic pathology was recorded from all available radiographs from the same day. A pattern considered consistent with AP was defined as evidence of lung consolidation or an alveolar pattern in the ventral lung lobes.

Six independent variables were evaluated for their potential association with death before discharge and overall survival in these patients. Five were categorical variables as follows: whether the animal’s age at the onset of clinical signs exceeded 13 months (an age approximating skeletal maturity across all breeds\(^\text{32}\)), the body weight at initial examination (categorized as < 10 kg [< 22 lb], 10 to 25 kg [22 to 55 lb], or > 25 kg), the presence of evidence of undernutrition, the presence of radiographic evidence of AP, and the administration of drugs used to treat and prevent esophagitis. Patients were deemed to have received drugs for the treatment of esophagitis if they had been pre-
scribed H₂-receptor antagonists, sucralfate, omeprazole, or prokinetics. The sixth variable, the RED, was modeled as a continuous variable, as there is no information available in the literature nor obvious biologically relevant cutoff to distinguish between small and large REDs. These 6 factors were chosen because their effects were considered likely to be independent of one another and because they were either considered by the authors or mentioned in the literature as being potentially associated with prognosis.

Outcome data—Owners and referring veterinarians were contacted for follow-up information if this was not available from the medical records. Outcome data included survival to discharge, number of days of hospitalization, and dates and causes of death. The cause of death (if known) was recorded as related to ME (including deaths from AP or related complications) or unrelated to ME. Whether the patient died or was euthanatized was also recorded. If a dog was subsequently lost to follow-up, the date of the last visit to the veterinarian was recorded, and these dogs were subsequently right censored from survival analyses on that date. Animals alive at the end of the study (October 2007) were also right censored.

The survival time was defined as the date of diagnosis of ME (date of radiography) to the date of death. The survival time was defined as the date of diagnosis of ME (date of radiography) to the date of death.

Statistical analysis—Statistical analysis was performed with standard statistical software. Statistical significance was defined as values of P < 0.05. The MSTs were calculated by use of Kaplan-Meier survival curves. Putative risk factors for death before discharge (outcome variable: survived to discharge or not) were assessed individually by use of univariable binary logistic regression analysis. Variables with a value of P < 0.25 in the univariable analysis were offered to a multivariable logistic regression model by use of a forward and backward stepwise selection procedure.

Putative risk factors associated with overall survival were evaluated individually by use of Cox proportional hazards models. Variables univariably screened as significant at P < 0.25 were carried forward to a multivariable analysis. The multivariable model was created by use of forward and backward stepwise selection. The proportional hazards assumption was evaluated by use of the scaled Schoenfeld residuals. The assumption of independent censoring was assessed by refitting the final model, assuming complete positive and negative correlations between censoring and death. The resulting coefficients and standard errors were then examined for gross changes. The overall goodness of fit of the final model was evaluated graphically by assessment of the distribution of the Cox-Snell residuals.

Results

Seventy-one patients fulfilled the inclusion criteria. Twenty-four breeds were represented, and 11 dogs were crossbreeds. Thirty-six dogs were male (11 castrated) and 35 were female (19 spayed). The most common breeds identified were German Shepherd Dogs (n = 14 [20%]), Golden Retrievers (6 [8%]), Great Danes (6 [8%]), Labrador Retrievers (4 [6%]), and Irish Setters (3 [4%]). The median age of the dogs at diagnosis was 6 years (range, 3 months to 12.7 years). The dogs weighed between 3.4 and 71.8 kg (7.5 and 158.0 lb) at initial examination (median, 25.0 kg). For 2 dogs, the weight at initial examination was not known.

Eighteen (25%) dogs included in the study were sedated for radiography. All sedated dogs were given acepromazine, and most (n = 17) were also given an opioid (butorphanol tartrate [12], buprenorphine hydrochloride [3], methadone [1], or pethidine hydrochloride [meperidine, 1]). Four (6%) dogs did not have vomiting or regurgitation reported at initial examination, but 3 had radiographic evidence of persistent ME for 15, 16, and 1,650 days, and 1 had gross esophageal dilation at necropsy performed the day after the radiographs were obtained.

The RED ranged from 0.2 to 1.5 (median, 0.58). The RED was measured in 68 of the 71 dogs, and ranged from 0.16 to 1.46 (median, 0.58). Median RED for dogs that survived to discharge (0.59; range, 0.16 to 1.46) was not significantly (P = 0.49; odds ratio, 0.46; 95% CI, 0.05 to 4.17) different from median RED for dogs that died before discharge (0.56; range, 0.41 to 1.32). Radiographic changes consistent with AP were present in 32 (45%) patients.

Seventeen (24%) dogs had diseases that were thought by the attending clinician to be causally associated with ME. These included 14 dogs with myasthenia gravis, 2 dogs with generalized neuromuscular disease, 1 dog with both ME and Horner syndrome that developed following cervical surgery (and presumed traumatic vagal injury), and 1 dog with CNS lymphoma in which the ME resolved following chemotherapy. Myasthenia gravis was diagnosed on the basis of compatible clinical signs and positive edrophonium response testing, acetyl choline receptor antibody titers, or both. No dogs in this study were characterized as having hypoadrenocorticism or hypothyroidism by the attending clinicians.

The MST from diagnosis to death for all the patients was 90 days (range, 0 to 2,895 days; Figure 1). The

Figure 1—Kaplan-Meier survival curve for 71 dogs with generalized ME. Censored observations are denoted by vertical dashes. Dashed lines represent upper and lower 95% CIs. Time zero represents the date of diagnosis.
percentages of dogs alive at 10 days, 1 month, 1 year, 2 years, and 5 years were 75.2% (n = 53), 62.3% (44), 41.0% (29), 31.3% (22), and 22% (16), respectively (taken from the Kaplan-Meier survival curve). The Kaplan-Meier curve for overall survival showed a steep initial decline, with 37.7% (27) of dogs dead by 1 month after diagnosis, followed by slowing of the death rate.

Median duration of hospitalization was 2.5 days (range, 0 to 15 days). Nineteen (26.8%) patients did not survive to discharge from the hospital (euthanasia was performed in 14, and 5 died). Of 52 (73.2%) patients that survived to discharge, 11 were alive, 7 were lost to follow-up, and 34 had died by the end of the study. Of the 53 patients known to have died, 42 (79.2%) patients were euthanatized and 11 died. Forty-three (81%) of these patients died or were euthanatized because of factors related to either ME or AP.

The results of the univariable logistic regression analysis for the dogs that died prior to discharge and those that survived to discharge for the 6 potential risk factors indicated that the presence of radiographic evidence of AP was the only risk factor found to be significantly (P = 0.001; OR, 7.69; 95% CI, 2.22 to 25.00) associated with death before discharge (Table 1). A body weight of > 25 kg and an age at onset of clinical signs of > 13 months were also associated with death before discharge, with odds ratios > 1 (3.70 and 5.88, respectively), although the CIs were wide around these estimates. After the association with AP had been taken into account, no other factors remained significant in a multivariable model.

In the univariable analysis of the effect of 6 potential risk factors on overall survival, 2 factors were strongly associated with survival at the univariable level (values were considered significant at P < 0.05; Table 2). These were the absence of radiographic evidence of AP (Figure 2) and an age of ≤ 13 months at the onset of clinical signs (Figure 3). In addition, body weight > 25 kg and evidence of undernutrition had positive hazard ratios. However, only an age of > 13 months at the onset of clinical signs and radiographic evidence of AP remained in the multivariable model, with adjusted hazard ratios of 6.38 (P < 0.001) and 2.21 (P < 0.01), respectively. The assumption of independent censoring was evaluated and was found to hold for the final model.

Table 1—Results of logistic regression analysis for 71 dogs with ME that died prior to discharge and those that survived to discharge and association with 6 potential risk factors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Total No. of dogs in group (% of total)</th>
<th>No. of dogs dying before discharge (n = 19)</th>
<th>No. of dogs surviving to discharge (n = 52)</th>
<th>Odds ratio of dying before discharge (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of clinical signs</td>
<td>≤ 13 mo</td>
<td>14 (19.7)</td>
<td>1</td>
<td>13</td>
<td>5.88 (0.73–50.00)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>&gt; 13 mo</td>
<td>57 (80)</td>
<td>18</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight at initial examination</td>
<td>&lt; 10 kg</td>
<td>8 (11.2)</td>
<td>1</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10–25 kg</td>
<td>26 (36.6)</td>
<td>5</td>
<td>21</td>
<td>1.67 (0.17–16.67)</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>&gt; 25 kg</td>
<td>35 (49.2)</td>
<td>12</td>
<td>23</td>
<td>3.70 (0.40–33.33)</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Data unavailable</td>
<td>2 (2.8)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of undernutrition</td>
<td>Absent</td>
<td>34 (47.9)</td>
<td>11</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>37 (52.1)</td>
<td>8</td>
<td>29</td>
<td>1.09 (0.38–3.13)</td>
<td>0.87</td>
</tr>
<tr>
<td>Radiographic evidence of AP</td>
<td>Absent</td>
<td>39 (54.9)</td>
<td>4</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>32 (45.1)</td>
<td>15</td>
<td>17</td>
<td>7.69 (2.22–25.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>Drugs to prevent or treat esophagitis</td>
<td>Not administered</td>
<td>32 (45.1)</td>
<td>8</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Administered</td>
<td>39 (54.9)</td>
<td>11</td>
<td>28</td>
<td>0.63 (0.23–1.82)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Values of P < 0.05 were considered significant. To convert kilograms to pounds, multiply value by 2.2.
— = Analysis not performed.

Table 2—Results of the univariable analysis of 71 dogs with ME and the effect of 6 potential risk factors on overall survival time.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Median (range) survival time (d)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of clinical signs</td>
<td>≤ 13 (n = 14)</td>
<td>2,381 (0–2,895)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>&gt; 13 (n = 57)</td>
<td>62 (0–2,482)</td>
<td>5.23 (2.02–13.57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body weight at initial examination</td>
<td>&lt; 10 (n = 8)</td>
<td>511 (1–1,814)</td>
<td>0.91 (0.33–2.51)</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>10–25 (n = 26)</td>
<td>716 (0–2,895)</td>
<td>2.16 (0.84–5.60)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>&gt; 25 (n = 35)</td>
<td>61 (0–2,854)</td>
<td>1.67 (0.44–3.35)</td>
<td>0.70</td>
</tr>
<tr>
<td>Evidence of undernutrition</td>
<td>Absent (n = 34)</td>
<td>150 (0–2,895)</td>
<td>1.22 (0.44–3.35)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Present (n = 37)</td>
<td>86 (0–2,895)</td>
<td>1.14 (0.66–1.96)</td>
<td>0.63</td>
</tr>
<tr>
<td>RED</td>
<td>NA (n = 68)</td>
<td>589 (0–2,895)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Radiographic evidence of AP</td>
<td>Absent (n = 39)</td>
<td>19 (0–1,749)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Present (n = 32)</td>
<td>261 (1.50–5.56)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Drugs to prevent or treat esophagitis</td>
<td>Not administered (n = 32)</td>
<td>90 (0–2,895)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Administered (n = 39)</td>
<td>86 (0–1,814)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

NA = Not applicable.
See Table 1 for remainder of key.
The Kaplan-Meier curve for dogs with AP at diagnosis (Figure 2) showed a very steep initial decline in the immediate days after diagnosis, followed by a slowing of the death rate, which then mirrored the curve for dogs without AP.

Discussion

In the present study, only radiographic evidence of AP and the age at onset of clinical signs were significantly associated with survival, and this should be considered when advising on prognosis in dogs with generalized ME. The patients in our study were similar to those described in previously published studies of ME with regard to breed and sex. The median age at diagnosis (6 years) for the dogs in the present study is younger than the mean age of 8.1 years reported by Gaynor et al; however, in that study, cases in which dogs developed ME at ≤ 6 months were excluded. Dogs in the present study were also lighter (median body weight, 25 vs 30 kg [55 vs 66 lb]), possibly again because of the lower median age. The median and range of the RED were similar to those reported by Wray and Sparkes. The prevalence of AP (45.1%) in the present study was lower than the reported prevalence of 60% to 71% in previous studies. Twenty-four percent of dogs had diseases that have been associated with the development of ME, which is similar to the 20% of dogs with primary nonobstructive extraoesophageal diseases identified in the study by Boudrieau and Rogers. However, this was a retrospective study and therefore an underestimation of the number of concurrent related diseases because of the incomplete panel of diagnostic tests performed in some animals was likely to occur. Acquired idiopathic ME is a diagnosis of exclusion that can be reached only after extensive investigations. For this reason, patients in the present study could not be accurately classified as idiopathic, and this term was not used.

In the present report, the overall MST was 90 days, more than double the 1-month MST in the 23 dogs treated medically by Harvey et al. The longer MST may result in part from the lower reported prevalence of AP in our study; however, this estimate of MST had a wide CI, and a larger number of patients would be needed to obtain a more precise estimate. The steep initial decline in the Kaplan-Meier curve for overall survival (Figure 1) was also seen in the Kaplan-Meier curve for patients with evidence of AP (Figure 2). It is likely that the death of dogs with evidence of AP accounts, at least in part, for the initial steep decline in the overall survival curve. Following the steep initial decline, the death rate began to slow and 22% of dogs were alive at 5 years after diagnosis, showing that survival in some animals with ME can be prolonged. It is possible that a proportion of these long-surviving animals recovered (information on recovery could not be collected in this study) because transient esophageal dysfunction, attributable to both esophagitis following anesthesia and unknown causes, has been reported to occur infrequently. It is also possible that long-surviving dogs in the present study were those with milder clinical signs. In those patients with persistent clinical signs of esophageal disease, the length of survival may depend on a combination of the severity or frequency of these signs and owner dedication, although further studies are needed to investigate this.

In the present study, we hypothesized that a positive association with overall survival would be found for dogs ≤ 13 months old (an age approximating skeletal maturity) at the onset of clinical signs. It was thought that in skeletally immature dogs, ongoing maturation of the esophagus and resulting improvement in their clinical signs would reduce their risk of death. Only 14 dogs in the present study were ≤ 13 months old at the onset of clinical signs, and only 1 died before...
discharge. This factor was associated with a positive odds ratio but was not significant ($P = 0.10$) for death before discharge, although, most likely because of the small number of dogs in the younger group and right censoring of over half of these animals, the study may have been underpowered to detect a difference. Dogs $> 13$ months old at the time of onset of clinical signs were $6.4$ times as likely to die at a given time point as were dogs $\leq 13$ months old.

In the present study, a higher body weight was expected to have a negative association with overall survival because these animals are harder to feed from an elevated position and are harder to manage if they have concurrent clinical signs such as weakness. Body weight of $> 25$ kg was associated with a positive odds ratio for death before discharge and a positive hazard ratio for overall survival, but neither reached significance ($P = 0.23$ and $P = 0.11$, respectively). In a study with a greater number of subjects, we speculate that this association would prove significant.

Evidence of undernutrition might have been expected to be associated with an increased risk of death, as this would suggest the patient was chronically debilitated. Approximately half of the patients in the present study had evidence of undernutrition, and although there was no observed association with death before discharge, there was a positive hazard ratio for overall survival. This suggests that an association between undernutrition and overall survival may be worthy of exploration in a larger study.

More marked esophageal dilation (manifesting as a greater RED) was expected to be associated with an increased risk of death, as this would suggest the patient was chronically debilitated. Approximately half of the patients in the present study had evidence of undernutrition, and although there was no observed association with death before discharge, there was a positive hazard ratio for overall survival. This suggests that an association between undernutrition and overall survival may be worthy of exploration in a larger study.

More marked esophageal dilation (manifesting as a greater RED) was expected to be associated with a poorer prognosis, as it may result in more severe clinical signs and might be less reversible. Additionally, it has been suggested that this is negatively associated with survival in congenital ME. However, the median RED of dogs dying before discharge and surviving to discharge was similar for the present study, and no significant association with death before discharge was identified. Likewise, no association with overall survival was found.

Both statistical and biological reasons for the absence of detection of an association are possible. The small range and the variability of possible values for the RED for the dogs in this study reduced the likelihood of demonstrating a significant association. Additionally, the degree of esophageal dilation may vary with time, patient positioning, phase of respiration, amount of food retained in the esophagus, and sedation, and although it is tempting when examining radiographs and considering prognosis to be influenced by the degree of esophageal distention, the present study found no evidence to support this.

The presence of AP on initial radiographic examination was expected to have a positive association with death before discharge, as it is known that AP can be a severe or even fatal complication of ME. Twenty-seven percent of dogs in the present study did not survive to discharge, and of these, 79% had AP. Aspiration pneumonia on the initial radiographic examination was found (on the basis of the odds ratio of the univariable logistic regression) to be associated with a $7.69$-fold increase in the risk of dying before discharge (Table 1). Dogs with AP on initial radiographic examination were also found (on the basis of the adjusted hazard ratios in the multivariable model) to be $2.21$ times as likely to die by a given time point as dogs without AP. The association of AP with overall survival appears from the Kaplan-Meier curve (Figure 2) to be largely attributable to a dramatic loss of patients in the early days following diagnosis, after which the curves appear to mirror one another. This is interesting because it suggests that dogs that recover from AP identified at initial examination are no longer at an increased risk of dying, compared with the dogs that do not have AP when first examined.

Drugs to treat esophagitis are often administered to patients with ME, as esophagitis and ME can occur concurrently. In many patients with ME, esophagoscopy is not performed because of the perceived increased risk of AP in these patients during or following general anesthesia. The association between the administration of these drugs and survival was of interest; however, no evidence of a significant association with either death before discharge or overall survival was found.

The present study was retrospective in nature and, as a result, has a number of limitations. Despite inclusion of patients examined over a long period, the number of patients was relatively small, as is often the case with studies of rarer diseases; therefore, the power to detect significant associations between exposures and outcomes could be a limitation.

Most of the dogs in the present study were euthanized, which would reduce the calculated MST, compared with what would be seen if the disease were allowed to progress to its natural endpoint.

No differentiation was made between dogs dying of ME or AP and those dying of other diseases, as it can be difficult to retrospectively determine the cause of death from owners. The majority ($> 80\%$) of owners in this study stated that ME or AP was the cause of death; therefore, this is unlikely to affect the study’s findings.

References