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# Use of a national identification database to determine the lifetime prognosis in cattle with necrotic laryngitis and the predictive value of venous $pCO_2$

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**Background:** Necrotic laryngitis, caused by *Fusobacterium necrophorum*, frequently requires surgical intervention (laryngostomy) in the chronic stage.

**Hypothesis/Objectives:** To determine survival until slaughter of cattle surgically treated for necrotic laryngitis and to identify predictors of mortality.

**Animals:** A total of 221 cattle diagnosed with necrotic laryngitis by laryngoscopy and surgically treated

**Methods:** Retrospective cohort study. Clinical records were matched with the national cattle identification, registration, and movement database. Information on possible predictors including clinical examination, biochemistry, and surgery was collected. A multivariable Cox proportional hazard model was used to identify predictors of mortality.

**Results:** The overall survival rate was 65.2% and 58.6% of the animals with a completed life cycle could be slaughtered. Animals <6 months old experienced significantly higher mortality risk (hazard ratio [HR], 2.0; 95% confidence interval [CI], 1.1-3.5). The venous partial pressure of carbon dioxide ($pCO_2$; HR, 2.4; 95% CI, 1.4-4.2) at a 64.5 mm Hg cut-off was most significantly associated with mortality. Sensitivity and specificity of the final model consisting of age and $pCO_2$ were 49.1 and 86.4%, respectively. Instead of $pCO_2$, total carbon dioxide ($TCO_2$) could also be used, with similar diagnostic accuracy.

**Conclusions and Clinical Relevance:** The lifetime prognosis for chronic necrotic laryngitis in cattle with surgical intervention appears fair. Age, venous $pCO_2$ and $TCO_2$ are easily accessible predictors of survival to support owners and veterinarians in their decision process of whether or not to operate and to identify high risk animals that require more intensive follow-up.

KEYWORDS

*Fusobacterium necrophorum*, laryngostomy, prognostic factors, respiratory disease, survival analysis

## 1 | INTRODUCTION

Necrotic laryngitis (calf diphtheria, laryngeal necrobacillosis) is a necrotic inflammation of the larynx in cattle caused by *Fusobacterium necrophorum*, a normal inhabitant of the bovine respiratory and

**Abbreviations:** BE, base excess; CI, confidence interval; ID, identification; HR, hazard ratio; $pCO_2$, partial pressure of carbon dioxide; $pO_2$, partial pressure of oxygen; ROC, receiver operating characteristics; $TCO_2$, total carbon dioxide; R, range; SD, standard deviation.

intestinal tract.[1,2] It is among the more frequent causes of inspiratory dyspnea and stridor in cattle, and the incidence of necrotic laryngitis was estimated to be 1%-2% in United States feedlot cattle and 0.1 and 0.8% in dairy and Belgian blue beef veal calves, respectively.[2,3] It is generally accepted that the disease begins with mechanical mucosal lesions in the larynx, which are colonized by *F. necrophorum*. Cattle breeds with a more narrow larynx and relatively smaller lung volume (eg, Belgian blue) develop higher air velocity at the level of the larynx, which predisposes them to mucosal lesions and subsequently necrotic laryngitis.[4] Necrotic laryngitis is frequently only detected when clinical signs of dyspnea with stridor are evident. In this more chronic disease stage, response to systemic antimicrobial and anti-inflammatory treatment is generally poor.[5] Surgical intervention is therefore often needed in these cases, and tracheotomy,[6] tracheostomy,[7,8] laryngotomy,[9] laryngostomy,[10,11] and tracheolaryngostomy[7] have been described, with variable outcomes.

For food animal owners, the decision to operate very much depends on the balance between the cost of surgery and the likelihood of recovery for the animal. Economic recovery implies that the animal can be slaughtered, either immediately after the antimicrobial withdrawal period or preferentially after a normal productive life as a breeding or fattening animal. To date, for practical reasons, only the short term prognosis is reported for many surgical interventions in cattle, mostly for only a relatively limited number of cases. For laryngostomy to treat necrotic laryngitis, outcome is reported until discharge,[9,10] and up to a maximum of 1 year.[11] In contrast, the lifetime prognosis, which signifies prognosis for economic harvest (slaughter) in this context, is what truly matters to the producer. Ideally, one should be able to determine the lifetime prognosis for a given animal based on predictors that could be measured upon admission for surgery. Both clinical signs and blood chemistry variables can be suitable predictors. To date, neither the lifetime prognosis nor predictors of increased mortality risk have been identified for laryngostomy to treat chronic necrotic laryngitis or for any other obstructive processes of the upper airways in cattle. This information would make a more individualized prognosis possible, which would better serve the client in decision making about whether to operate or not.

Therefore, the objectives of our study were to determine long term survival until slaughter of cattle surgically treated for necrotic laryngitis and to identify predictors of premature mortality after surgery.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design, data collection, and selection procedure

A retrospective cohort study was conducted, based on the patient records of the large animal clinic of the Faculty of Veterinary Medicine, Ghent University. All cattle with the diagnosis necrotic laryngitis, admitted to the hospital between January 1, 2008 and April 1, 2016 were included in the primary database (primary inclusion criteria). All cases were confirmed by laryngoscopy. Information on possible predictors was collected from 3 distinct records, namely patient record (clinical examination and blood chemistry results, measured upon arrival to the clinic), surgery record and hospitalization record. Primary exclusion criteria included necrotic laryngitis that was not surgically treated and absence of complete official ear tag identification (ID) number. Data from the clinical records were matched by the official ear tag ID with the national cattle identification, registration and movement database (SANITRACE, Animal Health Service Flanders (DGZ) and Federal Agency for the Safety of the Food chain, Torhout/Brussels, Belgium). The date of birth, breed, sex, whether the animal has been sold after surgery, its final destination (slaughterhouse, export or destruction facility; ie, mortality) and the date of this event were recorded. Secondary exclusion criteria after this match were wrong ear tag ID recorded on the patient record, foreign calves not registered on a Belgian cattle farm and animals for which no definitive destination could be retrieved. After this selection procedure, the final study population ($n = 221$) was obtained. Sample size calculations showed that the number of events (mortality) in the data set ($n = 78$), allowed identification of a hazard ratio (HR) of 2 or 0.5 between the groups of exposed and nonexposed for the risk factor, with a 30/70 proportion of the subjects in both categories of the risk factor, with 95% confidence and 80% power.

Venous blood gas analysis and determination of sodium, potassium, calcium, chloride, and glucose (oxidase method) were performed using the same automated blood gas analyzer (Rapidpoint 405, Siemens, Germany) in all cases, without temperature correction. Total carbon dioxide ($TCO_2$) was calculated according to the following formula: $TCO_2$ (mmol/L) $= [HCO_3^-] + 0.03 \times pCO_2$.[12] Anion gap was calculated as $(Na^+ + K^+) - (Cl^- + HCO_3^-)$. Packed cell volume (PCV) was determined by centrifugation (5588 rpm; 5 minutes). All animals were surgically treated either by laryngostomy or emergency tracheotomy and placement of a tracheotube. The laryngostomy and tracheotomy were performed as previously described.[6,7,10,11] Different anesthetic protocols were used, based on the live weight of the animal. For calves $< 300$ kg, sedation with xylazine, epidural, and local anesthesia with procaine 4% was used most frequently.[11] Larger animals were preferentially operated under inhalation anesthesia.

### 2.2 | Statistical analysis

Data were entered in a worksheet (Excel, Microsoft Inc, Washington) and transferred to a statistics program (SAS 9.4; SAS Institute Inc, Cary, North Carolina) for descriptive and statistical analysis. The unit of analysis was the individual animal. A Cox proportional hazards model (PROC PHREG) was built with mortality as the outcome parameter (event). The time between surgery and occurrence of mortality was defined as survival time and mortality as the event. Right censoring was done for each animal that had not died before the day of slaughter (end of observation period). No animals originated from the same farm and no other information on potential clustering was available. Therefore, no frailty model was used to correct for hierarchical dependence. The model building procedure was as follows: first, all predictors were tested univariably. Continuous predictors were tested as continuous variables and as categorical ones (based on quartiles and construction of a binary variable based on a cut-off determined by receiver

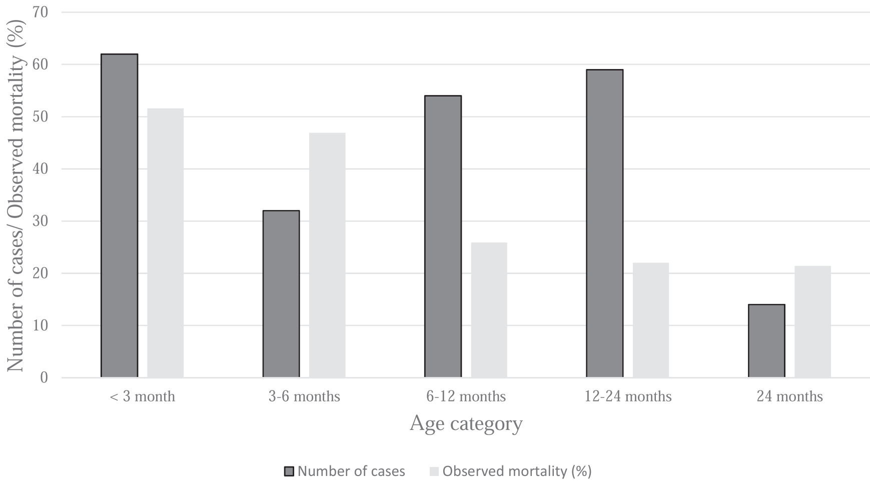


**FIGURE 1** Overview of the number of surgically treated cases of necrotic laryngitis in cattle and their mortality risk at Ghent University (2008–2016), stratified by age category.

operating characteristics (ROC) curve analysis. All variables were tested in the proportional hazards model for significance and those with $P < .20$ were selected for multivariable modeling.

For significant predictors, the relationship with mortality was visualized by means of Kaplan-Meier survival curves (PROC LIFETEST) and a log-rank test was performed. Continuous predictors were tested both continuously, in quartiles, and as binary variables. Receiver operating characteristics (ROC) curves were made for significant continuous predictors, to determine an optimal cut-off point based on the Youden's index. Pearson's and Spearman's rho correlations were calculated, and if >0.60, only the most significant predictor was added to the multivariable model. The final multivariable model was built in a stepwise backwards manner, gradually excluding nonsignificant variables. Next, all biologically relevant 2-way interactions of significant fixed effects were tested. Significance was set at $P < .05$. Wald's test was used to assess parameter estimate significance. Visual inspection of the log-cumulative hazard plots and construction of time-varying covariates were used to evaluate the proportional hazard assumption. Diagnostic accuracy (sensitivity and specificity) was determined by means of logistic regression (PROC LOGISTIC) with the default probability of 0.5. Linear regression (PROC MIXED) was used to explore the relationship between partial pressure of carbon dioxide ($pCO_2$) and other predictors. All values are presented as mean ± standard deviation (SD).

## 3 | RESULTS

### 3.1 | Descriptive results

Of the initial 239 records meeting the inclusion criteria in the 8-year study period, 221 could be matched with the national database. The annual number of admitted cases in the period 2008–2011 ranged between 33 and 37 cases, whereas this number was much lower from 2012 to 2016 (range, 16–24 cases per year). The study population consisted mainly of Belgian Blue beef cattle (96.8% [214/221]) and other breeds were Maine Anjou (n = 1), Holstein Friesian (n = 2) or crossbreds (Maine Anjou crossed with Belgian Blue [n = 1]). There were slightly more males than females in the dataset (55.5 and 44.5%, respectively). The mean age at admission (n = 221) was 306.7 days ± SD 340.9 (range [R], 14–3396) and the animals (n = 151) had a mean weight of 243.7 ± 170.2 kg (median [M], 202.0; R, 37–770). Age distribution and respective mortality risk are shown in Figure 1. On average, the animals had been showing signs for 24.5 ± 28.7 days (M, 14; R, 1–244). Upon admission 54.6% (65/119) of the animals showed marked inspiratory and expiratory dyspnea with stridor, 12.6% (15/119) had only inspiratory dyspnea and 32.8% (39/119) had a normal breathing pattern. Mean respiratory rate and heart rate were 49 ± 20/min. (R, 20–172) and 93.±27/min (R, 40–150), respectively. Rectal temperature averaged 39.6 ± 0.8°C (R, 37.3–42.4). Laryngoscopy showed partial and total absence of arytenoid movement in 85.1% (40/47) and 14.9% (7/47) of the cases, respectively. The arytenoids were severely swollen in 90.8% (109/120) of the cases and moderately swollen in 9.2% (11/120). Necrotic tissue could be visualized in 84.1% (37/44) of the cases. Of the calves, 58.1% (93/160) were hypercapnic on venous blood ($pCO_2 > 51$ mm Hg) and 11.9% (19/160) had too low $pCO_2$ (<41 mm Hg). Of the animals, 24% (37/154) were acidemic (pH < 7.35), 22.7% (35/154) alkalotic (pH > 7.45), and the majority (53.2% [82/154]) had normal venous pH. Further details on clinical examination, blood gas analysis, and electrolytes are presented in Table 1. Laryngostomy was performed in 95% (210/221) of cases and tracheotomy in only 5% of cases (11/221).

### 3.2 | Survival analysis

Of the 221 cases, 49.3% (109/221) were slaughtered, 34.8% (77/221) died, 1.4% (3/221) were exported and 14.5% (32/221) were still alive at the time of analysis. The overall survival rate was 65.2% (Figure 2). Of all animals that had completed their life cycle, 58.6% (77/186) could be slaughtered. The majority (approximately 20%) died in the first 60 postoperative days (Figure 2) and 6.3% (14/221) died at the clinic in the first year post-operative period, 30.3% (67/221) died, but detailed information on the cause of death was not available. The median survival time was 340.7 ± 298.3 days (R, 16–2201) for slaughtered

**TABLE 1** Results of the univariable survival analysis[a] for potential categorical predictors of mortality after surgical treatment of laryngeal necrobacillosis in cattle (221 cases)

| Parameter | Category | Observed mortality (%) (number/total) | *P*-value |
|---|---|---|---|
| Breed | Belgian Blue | 35.5 (76/214) | .31 |
| | Other | 0 (0/4) | |
| Sex | Female | 32.7 (32/98) | .09 |
| | Male | 36.1 (44/120) | |
| Age | <6 months | 50.0% (47/94) | <.001 |
| | >6 months | 23.6% (30/127) | |
| Season of admission | | | .17 |
| | Winter (ref.) | 36.6 (15/41) | |
| | Spring | 40.8 (31/76) | .76 |
| | Summer | 35.8 (19/53) | .84 |
| | Autumn | 23.5 (12/51) | .10 |
| Antimicrobial class of the first treatment | | | .14 |
| | Beta-lactam antibiotics | 30.7 (23/75) | .26 |
| | Macrolides | 47.6 (20/42) | .07 |
| | Others (ref.) | 16.7 (4/24) | |
| Cortisone treatment | No | 30.6 (15/49) | .42 |
| | Yes | 34.4 (33/96) | |
| Breathing type | | | .08 |
| | Normal (costo-abdominal) (ref.) | 46.2 (18/39) | |
| | Inspiratory dyspnea | 53.3 (8/15) | .72 |
| | Mixed dyspnea | 30.7 (20/65) | .06 |
| Dyspnea | No | 46.2 (18/39) | .16 |
| | Yes | 35.0 (28/80) | |
| Body condition Score | Good (scores 3 and 4) | 39.3 (44/112) | .86 |
| | Moderate and thin (scores 2 and 1) | 37.5 (3/8) | |
| Spontaneous cough | No | 38.5 (25/65) | .29 |
| | Yes | 35.0 (14/40) | |
| Nasal discharge | | | .54 |
| | None (ref.) | 42.6 (29/68) | |
| | Serous | 32.4 (12/37) | .27 |
| | Mucoid to purulent | 38.5 (5/13) | .77 |
| Swollen submandibular lymph nodes | No | 39.2 (20/51) | .72 |
| | Yes | 30.0 (3/10) | |
| Swollen retropharyngeal lymph nodes | No | 35.4 (17/48) | .64 |
| | Yes | 42.9 (3/7) | |
| Lung ausculation left thorax | Normal | 36.4 (8/22) | .48 |
| | Abnormal | 35.6 (21/59) | |
| Lung ausculation right thorax | Normal | 31.6 (6/19) | .55 |
| | Abnormal | 32.8 (19/58) | |
| Laryngeal reflex | Negative | 43.8 (7/16) | .68 |
| | Positive | 34.8 (24/69) | |
| Tracheal reflex | Negative | 37.8 (14/37) | .88 |
| | Positive | 39.5 (15/38) | |
| Abduction of the arytenoids | Normal or slight reduction | 14.3 (1/7) | .40 |
| | Complete absence | 40.0 (16/40) | |

(Continues)

**TABLE 1** (Continued)

| Parameter | Category | Observed mortality (%) (number/total) | *P*-value |
|---|---|---|---|
| Swelling of arytenoïds | Normal to moderate | 27.3 (3/11) | .32 |
| | Severe | 45.0 (49/109) | |
| Presence of necrotic tissue in the larynx | No | 43.8 (7/16) | .83 |
| | Yes | 42.1 (37/88) | |
| Emergency tracheotomy | No | 33.5 (63/188) | .14 |
| | Yes | 42.4 (14/33) | |
| Surgical procedure | Tracheotomy | 45.5 (5/11) | .14 |
| | Laryngostomy | 34.3 (72/210) | |
| Surgical experience | | | .58 |
| | ECVS diplomates (ref.) | 18.2 (2/11) | |
| | ECVS residents | 34.7 (26/75) | .30 |
| | Nonboard-certified surgeons | 33.3 (6/18) | .41 |
| Sold in the postsurgical follow-up period | No | 38.6 (61/158) | .16 |
| | Yes | 25.4 (16/63) | |
| $pCO_2$ (mm Hg) | <64.5 | 24.6 (29/118) | <.001 |
| | >64.5 | 66.7 (28/42) | |
| $TCO_2$ | <34.3 | 24.2 (24/99) | <.001 |
| | >34.3 | 55.6 (30/54) | |

Abbreviation: ECVS, European College of Veterinary Surgeons.
[a]Cox proportional hazards model.

animals and 189.3 ± 349 days (R, 1–2107) for animals that died. The mean age at slaughter was 837.8 ± 421.3 days (R, 115–2628).

In the univariable analysis, different factors showed significant association with mortality, such as age, body weight, rectal temperature, and several venous blood gas analysis parameters ($pCO_2$, $pO_2$, base excess, bicarbonate, $TCO_2$ and potassium; Tables 1 and 2). Younger and lighter animals had increased mortality risk. All of the above mentioned blood parameters were highly correlated, and the multivariable model was built starting with the following parameters: age, sex, season, breathing type, anion gap, $pCO_2$ and potassium. To explore the possibilities of $TCO_2$, a second multivariable model was built, with the above parameters and $TCO_2$ instead of $pCO_2$. The final multivariable model consisted of age as a binary variable (<6 months; >6 months old) and either $pCO_2$ or $TCO_2$ (Table 3). Kaplan-Meier curves for significant predictors are presented in Figures 3 and 4. For every 5 mm Hg increase in $pCO_2$ above 32.6 mm Hg, the HR for mortality increased by 12.3% (CI, 3.0–22.4%; $P < .01$).

The ROC analysis identified a $pCO_2$ of 64.5 mm Hg and a $TCO_2$ of 34.3 mmol/L as the optimal cut-off points to predict mortality (area under the curve, 0.69; CI, 0.60-0.78; $P < .001$ and 0.65; CI, 0.55-0.74; $P < .01$), respectively. For venous $pCO_2$, animals above this threshold experienced a mortality risk of 66.7 versus 24.6% in animals under the cut-off (HR, 2.4; CI 1.4-4.2). Animals above the $TCO_2$ cut-off had a HR of 2.1 (CI, 1.2–3.7; Figure 4). The interaction between $pCO_2$ or $TCO_2$, respectively, and age was not significant ($P = .62$). Survival for different age and $pCO_2$ combinations is presented in Figure 4. Animals older than 6 months with $pCO_2$ below the cut-off had significantly better survival compared to the 3 other categories (Table 3). Sensitivity, specificity, and accuracy of the model consisting of age and $pCO_2$ added as binary variables were 49.1, 86.4, and 73.1%, respectively. For the model of age and $TCO_2$, sensitivity, specificity, and accuracy were 38.9, 88.9, and 71.2%, respectively. Increasing $pCO_2$ was significantly associated with increasing PCV (correlation coefficient [CC], 0.33; $P = .01$), base excess (CC, 0.51; $P < .01$) and bicarbonate (CC, 0.52; $P < .001$) and with decreasing body temperature (CC, −0.33; $P < .05$). The $pCO_2$ was not significantly associated with heart rate ($P = .92$), respiratory rate ($P = .54$) or potassium ($P = .90$).

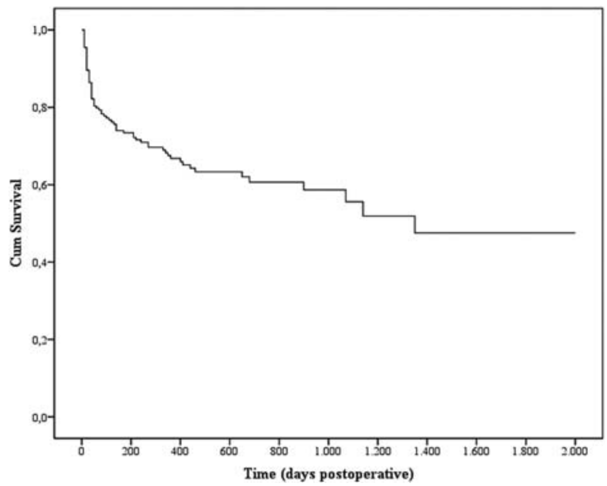


**FIGURE 2** Survival graph for mortality of necrotic laryngitis in cattle after laryngostomy and/or tracheotomy (221 cases; 2008–2016)

**TABLE 2** Descriptives and results of the univariable survival analysis[a] for potential continuous predictors of mortality after surgical treatment of necrotic laryngitis in cattle (221 cases)

| | | Mortality Mean ± SD (min.-max.) | | |
|---|---|---|---|---|
| Parameter | Calves (n) | No | Yes | *P*-value |
| Age at admission (days) | 221 | 354.0 ± 385.4 (16–3396) | 217.3 ± 211 (14–1099) | .04 |
| Body weight at arrival (kg) | 151 | 280.1 ± 169.0 (53–770) | 180.2 ± 156.4 (37–575) | .02 |
| Number of days seen with signs | 152 | 36.1 ± 25.9 (1–120) | 21.4 ± 33.6 (2–244) | .40 |
| Temperature at admission (°C) | 208 | 39.7 ± 0.8 (37.7–42.4) | 39.3 ± 0.9 (37.3–42) | <.01 |
| Heart rate (beats/minute) | 140 | 93 ± 29 (40–150) | 92 ± 24 (52–144) | .90 |
| Respiratory rate (breaths/minute) | 163 | 49 ± 21 (24–172) | 49 ± 29 (20–120) | .75 |
| pH | 155 | 7.4 ± 0.07 (7.2–7.5) | 7.4 ± 0.09 (7.2–7.8) | .28 |
| $pCO_2$ (mm Hg) | 160 | 52.3 ± 11.8 (32.6–96) | 62.5 ± 15.9 (34.2–97.5) | <.01 |
| $pO_2$ (mm Hg) | 149 | 38.4 ± 11.9 (20.5–97.7) | 33.7 ± 8.9 (17.8–62) | .04 |
| Base excess (mEq/L) | 158 | 6.0 ± 4.9 (7.3–19.1) | 8.4 ± 6.4 (−13–19.8) | .04 |
| Bicarbonate (mmol/L) | 154 | 29.8 ± 5.4 (3.6–42.4) | 32.8 ± 6.2 (20.2–46.7) | <.01 |
| $TCO_2$ (mmol/L) | 153 | 31.3 ± 5.5 (5.6–44.5) | 34.7 ± 6.4 (21.6–48.9) | <.01 |
| Sodium (mmol/L) | 72 | 134.4 ± 4.1 (124–142.7) | 134.8 ± 4.1 (128.7–145) | .89 |
| Potassium (mmol/L) | 72 | 4.0 ± 0.5 (3.2–6.1) | 4.4 ± 0.7 (3.3–6.7) | .02 |
| Ionized calcium (mmol/L) | 73 | 1.1 ± 0.1 (0.4-1.4) | 1.2 ± 0.1 (1.0–1.4) | .33 |
| Chloride (mmol/L) | 42 | 94 ± 3.4 (87–102) | 92.5 ± 5.4 (83–101) | .35 |
| Glucose (mg/dL) | 40 | 112.3 ± 35 (72–190) | 109.9 ± 60 (37–287) | .87 |
| PCV (L/L) | 130 | 32.1 ± 5.1 (24–48) | 33.2 ± 6.7 (22–48) | .39 |
| Anion gap (mmol/L) | 41 | 14.6 ± 6.8 (6.1–43.7) | 11.4 ± 6.2 (1.0–27.0) | .06 |

Abbreviation: SD, standard deviation.
[a]Cox proportional hazards model.

## 4 | DISCUSSION

Determining the long term prognosis by telephone inquiry to evaluate the outcome of a treatment is very time consuming and prone to reporting bias.[11,13,14] Currently, in most western countries, advanced food animal registration systems are available, which are either managed by governmental or nonprofit organizations, depending on the country. The availability of such registration systems opens the possibility to determine the lifetime prognosis of different disease events and treatments in food animals in a less time consuming and more accurate way. Our study is an example of how connecting different datasets, in this case national cattle registration data with hospital records, delivers valuable information on the long term success rate of a surgical treatment. A limitation of our study is its retrospective design, which inherently is affected by missing data. Because not all cases were retrieved (<2%), selection bias is possible. In addition, recent transport might have influenced certain signs at clinical examination upon admission. Because all hyperthermic animals were cooled before surgery, the effect of hyperthermia could not be properly evaluated.

In contrast to human and companion animal medicine, where prolongation of life is valued, in food animal medicine the focus is on having an economic return from the animal. Therefore, the decision to operate a food animal is mainly an economic one, carefully balancing the cost of the surgery against the possible production value of the animal in the event of survival. Our study found a survival rate of 65.2%. These results are comparable with reported survival rates of 58% and 60% in previous studies with identical surgical technique on 130[11] and 35[10] Belgian blue animals, respectively. The follow-up time in these studies ranged between 5 months and 1 year. In our study, the majority of mortalities appeared immediately after surgery or few weeks later. Therefore, the available short term prognosis after surgical intervention provides a reasonable estimate of the long term outcome of laryngostomy. However, a follow-up period of 1 year would still suggest that approximately 14% of the mortalities are missed. The prognosis was comparable to that of orthopedic surgery procedures such as internal fixation of long bone fractures in newborns (64%, 58 cases)[13] or external fixation of tibial fractures (64%, 55 cases).[14] It was better than resection of an intussusception (43%, 46 cases),[15] but worse than umbilical surgery (85%, 34 cases)[16] in calves. Shortly after surgery, suffocation, and aspiration pneumonia were the most common causes of death. The number of necrotic laryngitis cases admitted to the hospital approximately halved from 2012 on, without any effects on

**TABLE 3** Cox regression model output on $pCO_2$, $TCO_2$, and age as predictors of mortality after laryngostomy and tracheotomy to treat chronic necrotic laryngitis in calves (2008–2016)

| Variable | Category | Calves (n) | Mortality (%) | HR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|
| $pCO_2$ model | | | | | | |
| Age | <6 months | 66 | 51.5 | 2.0 | 1.1–3.5 | .01 |
| | >6 months | 92 | 22.8 | Ref. | | |
| $pCO_2$ (mm Hg) | <64.5 | 117 | 23.9 | 2.4 | 1.4-4.2 | <.01 |
| | >64.5 | 41 | 65.9 | Ref. | | |
| $TCO_2$ model | | | | | | |
| Age | <6 months | 66 | 51.5 | 2.0 | 1.2–3.6 | .02 |
| | >6 months | 87 | 23.0 | Ref. | | |
| $TCO_2$ (mmol/L) | <34.3 | 99 | 24.2 | 2.1 | 1.2–3.7 | <.01 |
| | >34.3 | 54 | 55.6 | Ref. | | |
| Combined model | | | | | | |
| >6 months and $pCO_2 < 64.5$ mm Hg | 77 | 16.9 | Ref. | | 0 | |
| <6 months and $pCO_2 < 64.5$ mm Hg | 41 | 39.0 | 2.2 | 1.1–4.5 | .04 | |
| <6 months and $pCO_2 > 64.5$ mm Hg | 27 | 74.1 | 5.0 | 2.5–10.0 | <.001 | |
| >6 months and $pCO_2 > 64.5$ mm Hg | 15 | 53.3 | 2.6 | 1.1–6.9 | .03 | |

Abbreviations: HR, hazard ration; $pCO_2$, venous partial pressure of carbon dioxide; $TCO_2$, total carbon dioxide.

postoperative survival. Possible explanations are earlier detection and more adequate antimicrobial treatment in practice or more confidence in practitioners to perform surgery in the field.

In our study, a series of clinical and biochemical variables could be evaluated. The mortality risk was approximately double in animals younger than 6 months. Most likely, these young animals must live for a longer period of time to reach reasonable slaughter weight, which increases the odds of breathing stoma closure and recurrence of laryngeal obstruction. They also might experience higher odds of comorbidities such as infectious pneumonia. Prediction of survival based on clinical signs did not appear possible. Respiratory rate and dyspnea were not significant predictors. Laryngoscopy has been recommended to confirm necrotic laryngitis, but its prognostic value for long term mortality has not been documented. In our study, no prognostic value could be attributed to the laryngoscopic findings. Possibly, the fact that all cases were judged as chronic and untreatable by the referring veterinarian may have created a subpopulation with severe lesions.

Arterial blood gas analysis and $pO_2$ determination traditionally have been recommended to evaluate acid-base disturbances in dyspneic persons, but with the exception of $pO_2$, a good correlation between arterial and venous parameters exists in healthy subjects, and repeatability is good for $pCO_2$.[17,18] Arterial $pCO_2$ has been associated with mortality in cases of exacerbation of chronic obstructive pulmonary disease in humans.[19] Venous blood is much more accessible, especially in cattle in which arterial puncture is not easy in unsedated animals. In our study, all blood test results influenced by respiratory acidosis (eg, $pCO_2$, $pO_2$, $TCO_2$, base excess, pH, potassium) were univariably associated with survival, but $pCO_2$ and $TCO_2$ were the best predictors. Increased $pCO_2$ signifies impaired ventilation and in response to hypercapnia, respiratory rate is increased. However, in our study no positive association between $pCO_2$ and respiratory rate was found. Most likely, because of the chronic nature of the disease, respiratory muscle fatigue was present, resulting in $CO_2$ retention.[20] The observed positive association between venous $pCO_2$ and PCV could be a consequence of dehydration or chronic hypoxia in severely ill animals, but most likely was a consequence of chronic hypoxia

Venous $pCO_2$ on hospital admission also has been identified as a predictive factor for mortality in calves with respiratory distress syndrome (surfactant deficiency).[21] Interestingly, the cut-off to optimally distinguish survivors from nonsurvivors in that calf study was 63.5 mm Hg, which is similar to the 64.5 mm Hg found in our study. However, the survival graphs of our study clearly show that $pCO_2$ and $TCO_2$ appear to influence survival in the long term (> 1 year postoperative). Unfortunately, no comparative information on the use of venous $pCO_2$

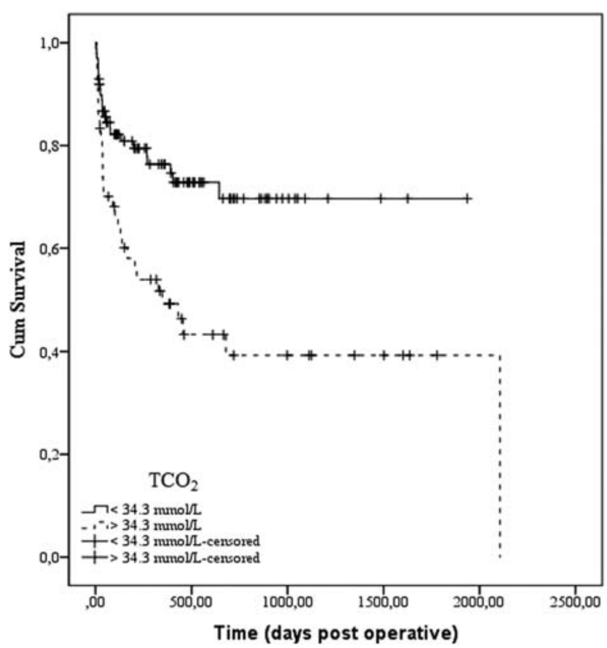


**FIGURE 3** Survival graph for mortality of necrotic laryngitis after laryngostomy and/or tracheotomy, stratified by venous $TCO_2$ (mmol/L) concentration upon admission (153 cases; 2008–2016; Log Rank test: $\chi^2 = 11.0$; df = 1; $P < .01$)

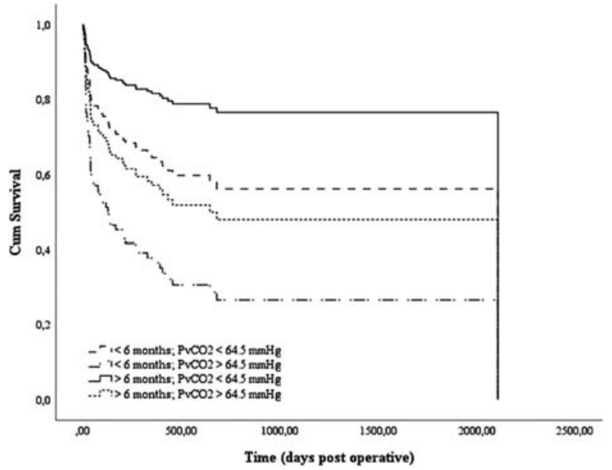


**FIGURE 4** Survival graph for mortality of necrotic laryngitis after laryngostomy and/or tracheotomy, stratified by age and venous $pCO_2$ (mm Hg) concentration upon admission (160 cases; 2008–2016; Log Rank test: $\chi^2 = 24.1$; df = 1; $P < .001$)

to predict mortality was available for any obstructive disease of the upper airways in animals or humans. In humans, venous $pCO_2$ was not associated with 1-year readmission and death rate in patients with acute dyspnea.[17] In contrast, $TCO_2$ ranging between 30 and 40 mmol/L (upper quartile; reference range, 24–29 mmol/L) upon admission signified a HR of 1.7 for mortality within 1 year in humans with acute dyspnea. Total $CO_2$ is not frequently used in veterinary medicine, especially not in cattle.[22] Total $CO_2$ has been suggested to be a better outcome predictor in the critically ill because it combines the respiratory and metabolic components and is less variable in nature than other blood gas parameters.[17] Given that $pCO_2$ also was a significant predictor, the respiratory component of the acid-base disorder appears predictive in these cases of necrotic laryngitis. Possible explanations for the poor long term outcome in these cases of necrotic laryngitis with high $pCO_2$, $TCO_2$, or both might be the presence of underlying pneumonia or other masked cardiopulmonary condition, persisting functional upper airway obstruction, or advanced respiratory muscle fatigue. No highly specific diagnostic tools such as thoracic ultrasonography[23] were used in our study to confirm underlying pneumonia or cardiovascular abnormality.

Our study showed that either model ($pCO_2$ with age or $TCO_2$ with age) can be useful in a clinical setting. Both models lack sensitivity, resulting in many false negatives. In contrast, they are quite specific predictors, resulting in <15% false positives, with $TCO_2$ performing slightly better on specificity. Venous $pCO_2$ already is an easily accessible prognostic parameter in a hospital setting, but availability of better priced portable blood gas analyzers might enable the use of this parameter on the farm. Recent evaluation of a portable device showed reliable results for $pCO_2$, but not for $TCO_2$.[24] Becasue calculated and measured $TCO_2$ generally correlate well, manually calculating $TCO_2$ for these devices might be an alternative.[12]

Predictors for a given outcome can be identified on 1 dataset, but should be externally validated on a second dataset in order to determine their true predictive value in practice.[25] Given the relatively rare nature of the studied disease, we currently did not have a sufficiently large dataset of new cases at our disposition. Therefore, the reported sensitivity and specificity of $pCO_2$ or $TCO_2$ and age as survival predictors is provisional and confirmation on another dataset is advisable. Model accuracy might be improved in the future by studying predictors for the main identified mortality causes (eg, aspiration pneumonia, suffocation, and breathing stoma closure) or by including additional blood parameters (eg, lactate or cardiac biomarkers).[21,26] With these models, high-risk patients can be identified, and measures to normalize $pCO_2$ before (eg, tracheotomy, treatment of underlying cardiopulmonary disease) and after (eg, wound care, and treatment of underlying cardiopulmonary disease) surgery can be taken to increase survival chances. Timely recognition of the disease and recognition of its severity by laryngoscopy are advisable to avoid animals being admitted for surgery in a hypercapnic state.

In conclusion, our study identified the value of connecting national cattle registration data with hospital records to determine the economically important lifetime prognosis of a disease or treatment. The prognosis of laryngostomy to treat chronic necrotic laryngitis in cattle can be regarded as fair. Age and venous $pCO_2$ or $TCO_2$ were identified as predictors of mortality and can be used by veterinarians to correctly inform cattle owners and identify animals in need of more intensive preoperative and postoperative care.

## CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

## OFF-LABEL ANTIMICROBIAL USE DECLARATION

Authors declare no off-label us of antimicrobials.

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

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