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Retrospective cohort study on diseases and risk factors associated with death in hospitalized neonatal foals

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Abstract

Background: The care of sick neonatal foals is labor-intensive and costly. Prediction of risk of death upon admission is often difficult but might support decision-making.

Objectives: To determine diseases and risk factors associated with death in neonatal hospitalized foals.

Animals: Two hundred twenty-two hospitalized foals, ≤7 days old.

Methods: Retrospective cohort study. Clinical and laboratory variables were evaluated for their association with death by means of Cox survival analysis and by classification and regression tree (CART) analysis.

Results: Most prevalent diseases were sepsis (43.9%), enteritis (14.0%), and omphalitis (9.0%). Case fatality rate was 33.3%. Neonatal sepsis significantly increased the risk of death (hazard ratio [HR] = 1.9; 95% confidence interval [CI] = 1.2-3.0; $P = .009$). Multivariable Cox regression in foals ≤7 days old revealed comatose mental state (HR = 2.9; 95% CI = 1.1-8.1; $P = .04$), L-lactatemia (≥373.8 mg/L [4.2 mmol/L]; HR = 4.4; 95% CI = 1.7-11.7; $P = .003$) and increased serum amyloid A (SAA; ≥2054 μg/mL; HR = 3.9; 95% CI = 1.2-12.7; $P = .02$) as risk factors for death, with a sensitivity and specificity of 7.5% and 95.7%, respectively. The CART analysis highlighted L-lactatemia, comatose mental state, and hypercapnia as risk factors for death, with a sensitivity of 38.1% and specificity of 86.1% after validation.

Conclusions and Clinical Importance: In this study sample, sepsis was associated with the highest risk of death. Identified risk factors such as SAA, L-lactate, and comatose mental state might guide veterinarians and owners in better decision-making for economic or welfare reasons. Frequently measured laboratory variables, such as blood glucose concentration and Immunoglobulin G, were not sensitive and specific enough to provide reliable decision support for survival estimation.

Abbreviations: Acc, accuracy; AUC, area under the curve; BUN, blood urea nitrogen; Ca, calcium; CART, classification and regression tree; CI, critically ill; Cl, chloride; FSS, foal survival score; FTP, failure of transfer of passive immunity; $HCO3^-$, bicarbonate; HR, hazard ratio; IgG, immunoglobulin G; K, potassium; M, median; MODS, multi-organ dysfunction syndrome; Na, sodium; NMS, neonatal maladjustment syndrome; NPV, negative predictive value; PA, polyarthritis; PAS, perinatal asphyxia syndrome; PCV, packed cell volume; PPV, positive predictive value; R, range; ROC, receiver operating characteristic; SAA, serum amyloid A; SD, standard deviation; Se, sensitivity; Sp, specificity.

KEYWORDS
blood culture, prognosis, sepsis, septicemia, survival analysis

1 | INTRODUCTION

Hospitalization in intensive care unit of neonatal foals is costly and time-consuming. Despite considerable progress in the care of hospitalized foals in recent years, the risk of death remains substantial, ranging between 20% and 60%.[1-5] Identifying prognostic factors for survival can improve evidence-based estimation of survival chances upon admission, reducing unnecessary animal suffering, minimizing hospitalization times, and maximizing the owner's return on investment. As a consequence, it enhances the owner's well-being through better preparation for a poor prognosis.[6-8] Multiple studies have explored risk factors associated with death in hospitalized (neonatal) foals.[2,8-11] An original foal survival score (FSS) was developed for hospitalized foals aged ≤4 days, considering multiple risk factors: cold extremities, prematurity, ≥2 infection/inflammation sites, decreased immunoglobulin G (IgG) levels, hypoglycemia, leukopenia. This score was then assessed by applying it to another group of foals, drastically decreasing the specificity. Sensitivity and specificity of both the original and adapted FSS (cut-off value ≥6 instead of ≥4, different age and group of foals) were reported to range between 96% and 97% and 28% and 71%, respectively.[4,12] A recent study demonstrated that the diagnostic performance of such scores substantially decreases when using another cut-off or when applying the score to foals from another setting, clinic or country.[12] The aforementioned studies did not report the prevalence of diseases for which young foals were hospitalized in neonatal care units and their respective survival chances. Often focusing only on a subset of diseases, particularly bacteremia/sepsis, which are important contributors to death.[13] While previous studies used logistic regression, survival analysis is regarded as the recommended method for the analysis of death.[2,4,9,14-16] Alternatively, a classification and regression tree (CART) analysis could offer a more accessible tool for survival prediction in practice or hospital settings.[17] To the authors' knowledge, this type of analysis has not yet been performed for death prediction in hospitalized foals. In previous work, comatose state, decubitus, hypothermia and the presence of pneumonia, have consistently been associated with death in neonatal foals.[4,5,18-21] In extension to a clinical prediction model, laboratory assays can aid in better prediction of survival. Especially point-of-care diagnostic tests have great potential to support decision-making as results are immediately available. Several biomarkers have been explored in foals for their association with death. Low IgG, increased L-lactate or serum amyloid A (SAA) levels, as well as low blood glucose concentration, have been demonstrated to be associated with death.[1,19,22] The first objective of this study was to determine which diseases affect neonatal foals (admitted to and hospitalized in a veterinary teaching hospital) most frequently and to report disease-specific death. The second objective was to identify risk factors upon admission, both clinical and blood variables, associated with death in hospitalized foals using both Cox survival and CART.

2 | MATERIALS AND METHODS

2.1 | Study design & animals

A retrospective cohort study was conducted based on the medical records of hospitalized foals in the veterinary teaching hospital of Ghent University. Inclusion criteria were foals aged ≤7 days hospitalized between May 2013 and September 2021. Foals with missing data were also included in the study as long as they met the inclusion criteria (see Table 3).

The sample size was determined based on the available records. In this study, 222 foals were included. To detect a hazard ratio (HR) of 2 (or 0.5) with 95% confidence and 80% power, taking into account that the proportion of subjects exposed to the risk factor is 0.3 while in the unexposed group it is 0.7, 78 observations per test group are needed. Hence, the study sample allowed to explore factors with 3 categories, meaning that a variable can show statistical significance when it is categorized into a maximum of 3 groups per variable (eg, leukocytes).

2.2 | Data collection

2.2.1 | Physical examination and ancillary diagnostic tests

Physical examination was performed upon admission, following the guidelines from McKenzie.[23] Signalment (breed, age, sex) and body weight (kg) were recorded. Based on information derived from the physical exam, 26 clinical risk factors were included; mental status (alert, lethargic, abnormal neurological signs, comatose), rectal temperature (°C), heart rate (bpm), respiratory rate (/min), arterial pulse strength (normal, strong, weak), heart auscultation (normal, systolic murmur, diastolic murmur, continuous murmur), lung auscultation (normal, wheezes, crackles), dyspnea, recumbency (lateral, sternal), mucosal color (pink, light pink, pale, hyperemic, icteric, cyanotic, petechia), capillary filling time (s), peripheral circulation (normal, reduced), enophthalmos (mm), nystagmus, palpebral reflexes, hypopyon, entropion (unilateral, bilateral), suckle reflex (absent, weak, strong), presence of wounds (local, diffuse), umbilicus (normal, umbilical hernia, swollen, swollen and wet and painful, swollen with pus and painful), fecal consistency (normal, pasty, moderately watery, watery mixed with blood or mucus), musculoskeletal (tendon retraction, tendon elongation, hoof maturity), dystocia, prematurity (days), and the presence of focal infections (omphalitis, arthritis, enteritis, and pneumonia). Transcutaneous ultrasonography was conducted to investigate the presence of enteritis, pneumonia and omphalitis using a 7.5 MHz probe (Esaote MyLab30 Gold, the Netherlands), with 70% propyl ethanol as a transducing agent. Information on previously administered

antimicrobial and anti-inflammatory treatment, as well as on parturition (dystocia, placentitis, red bag delivery or non-survival of the mare) was gathered from the history of the foal. After physical examination mean arterial blood pressure was determined non-invasively by an indirect oscillometric blood pressure device (Cardell Veterinary Monitor, 9401, Midmark, Florida) at the level of the tail (medial caudal coccygeal artery) with a cuff-to-tail size ratio of 2.5-3.5.[24] The mean of 5 measurements was used for analysis.

2.2.2 | Definitions

Laboratory analysis

Table 1 displays defintions of clinical terms related to neonatal foal health and conditions. Blood was sampled from the cephalic, medial saphenous or jugular vein using a 20G or 23G needle and 10-20 mL syringe. Heparin and EDTA tubes along with a clot activator tube were taken to collect plasma and serum samples. Blood gas analysis, glucose, L-lactate, and electrolytes (sodium [Na^+], potassium [K^+], calcium [Ca^{++}], chloride [Cl^-]) were analyzed by RAPIDPoint 405 and RAPIDPoint 500e (Siemens Healthcare, Beersel, Belgium) upon admission. Hematology and biochemical analysis were performed by the IDEXX ProCyte Dx Hematology Analyzer (IDEXX Europe B.V., Hoofddorp, The Netherlands) and IDEXX Catalyst One Chemistry Analyser (IDEXX Europe B.V., Hoofddorp, The Netherlands), respectively. The SNAP FOAL IgG test measured immunoglobulin G (IDEXX SNAP Foal IgG test, IDEXX Europe B.V., Hoofddorp, The Netherlands). SAA was determined by the Stablelab EQ-1 handheld reader (Zoetis B.V., Parsippany, New Jersey, United States) or Veterinary Medical Research & Development (VMRD) reader (Grovet B.V., Utrecht, The Netherlands) according to manufacturer's guidelines and reference values.

Blood culture

Blood for culture was collected from the jugular vein after aseptically preparing (clipping, scrubbing with chlorhexidine 4% and disinfection with 70% propyl ethanol). Sterile gloves, a 20G or 23G needle and 10-20 mL syringe were used for sterile sampling. Collected blood was aseptically injected within an aerobic enriched medium (BACTEC Plus Aerobic medium 8-10 mL and/or BD BACTEC Peds Plus medium 1-3 mL [BD, Erembodegem, Belgium]) with a new needle after disinfecting the cap. Subsequently, the blood culture bottle was aerobically incubated within an automated system at 35°C for detection of microbial growth (BACTEC FX, BD, Erembodegem, Belgium). Positive samples were further characterized by MALDI-TOF MS, VITEK or classical biochemical bacterial identification. If no microbial growth was detected after 5 days of incubation the samples were considered negative.

2.3 | Statistical analysis

Data were collected in a worksheet (Excel, Microsoft Inc, Washington) and transferred to a statistical program (IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp) for analysis.

TABLE 1 Definitions.

Neonatal foal	A foal ≤7 days old.
Critical illness	Having respiratory (dyspnea or respiratory rate >20/min), cardiovascular (heart rate <48 bpm or >100 bpm) or neurological dysfunction, separately or in combination,[62] with the addition of an abnormal rectal temperature, either below or above the reference interval (37.2°C-38.9°C).[59]
Septicemic foal	Foal that is critically ill + positive blood culture.
Bacteremic foal	Foal that has a positive blood culture in absence of clinical signs of critical illness.
Neurological dysfunction	Incoordination, head pressing, tetany, tremors, circling, opisthotonos or ataxia.
A comatose mental state	Characterized by a lack of responsiveness to external stimuli, including noxious, audible or visible stimuli. This state implies a profound depression of consciousness.
Normal fecal consistency	Characterized as moist.[60]
Neonatal maladjustment syndrome or Perinatal asphyxia syndrome	Impaired oxygen delivery to organs of the foal during birth, resulting in clinical signs such as apathy, difficulties/inability to stand, disorientation, ataxia, blindness, tremors, recumbency, and weakness.[61,63]
The peripheral circulation	Assessed based on cold extremities, capillary refill time, and prolonged filling of the jugular vein.
Pneumonia	Diagnosed based on the presence of consolidations visible on ultrasound.
Enteritis	Diagnosed based on thickening of the intestinal wall and oedema visible on ultrasound in combination with abnormal fecal consistency.
Impaired oxygen delivery	When pulmonary perfusion decreases to the point where the transport of oxygen to the uteroplacental unit is insufficient resulting in hypoxia of the foal.
Dystocia	Included red bag, placentitis, unknown breeding date, deceased mare.
Placentitis	Inflammation of the placenta.
Red bag delivery	Premature release of the placenta, releases before the amniotic fluid.
Failure of transfer of passive immunity	Present when SNAP Foal IgG test was <800 mg/dL.

To determine the risk of death of each of the separate foal diseases, a Cox survival analysis was performed. The outcome of interest was death (0/1), whereby time was defined as the time between admission and either discharge from the clinic (0) or death (1). Right censoring was done on the day of discharge. To identify risk factors associated with death, 3 different survival models were built; a first model only included clinical factors, a second one only laboratory variables and a third one combined both clinical and laboratory variables. The model-building procedure was as follows; in a first step, all variables were tested univariably for their association with death. All factors with less than 100 observations and with $P > .20$ were withheld for the multivariable model-building procedure. Among the factors exhibiting high levels of association, such as neutrophils, leukocytes, HCO_3^-, base excess, pH and venous pCO_2, only the most significant factors, namely leukocytes and pH, were included for further analysis. Next, the multivariable models were built stepwise backward, gradually excluding non-significant variables. Continuous variables were both tested continuously as well as categorically. Categories were obtained according to quartiles, deviations from normal reference values and binary using a cut-off as determined by receiver operating characteristics (ROC) curve analysis. For categorical variables, the original categories were grouped into larger categories with a minimum of 20 observations to allow model convergence. If not possible, categories were excluded from analysis. Correlations between significant continuous factors were tested using Pearson and Spearman correlation tests. When this correlation was ≥0.6, only the most significant variable was used for further modeling. For the categorical blood parameters, associations were tested using Chi-square for categorical variables. A causal web was drawn to facilitate identification of potential confounders or container variables. The proportional hazards assumption was checked by visual inspection of the log-cumulative hazard plots and construction of time-varying covariates. For significant predictors of interest, the relationship with death was visualized using Kaplan-Meier survival curves and a log-rank test was performed. Interactions between significant main factors were tested. For all models, significance was set at $P < .05$. All values are presented as mean ± standard deviation (SD) and median. Additionally, Kaplan-Meier survival graphs were built for biomarkers currently in use. As an alternative approach a CART analysis was performed. The decision trees were built with continuous variables as presented in Table 3. Variables that could be subjectively interpreted, such as lung auscultation, were excluded from the analysis because the between-observer agreement was low.[25] This decision tree method splits data with maximal homogeneity within a node until homogeneity or imposed stopping criteria in a node are reached with respect to the value of the objective variable. Impurity is indicated by the degree of non-homogeneous subset in a node and is measured by the Gini index. The minimum change in improvement was set at 0.0001. Growth limit was set at 10 observations in the parent node and 5 in the child node, whereby the maximum tree depth of the decision tree was determined at 4. The number of surrogates was set as automatic, to assure that the application had flexibility to incorporate surrogate predictors or alternative predictors, enhancing robustness and predictive accuracy of the model. Training and validation data were used to validate the tree. The dataset was split into 70% for training and 30% for validation. Diagnostic performance of the tree was estimated using diagnostic accuracy, sensitivity, and specificity.

3 | RESULTS

3.1 | Animals

In the dataset of foals ≤7 days, 222 were included with a mean ± SD and median age upon admission of 2.0 days ± 1.6 and 1.0 day, respectively (range [R], 0-6 days). Fifty-one point four percent (114/222) and 43.7% (97/222) were male and female, respectively. Sex was not reported for 5.0% (11/222) of the foals. The majority of the foals were Warmbloods 59.9% (133/222). Ponies, Thoroughbreds, and Draft Horses represented 0.9% (2/222), 1.4% (3/222), and 2.7% (6/222) of the cases, respectively. Other breeds represented 12.2% (27/222) of the foals, while in 23.0% (51/222) breed was not reported.

TABLE 2 Overview of diseases and their case fatality rate in 222 neonatal foals (≤7 days) using Cox survival analysis.

Disease	Disease prevalence (N)	Death % (N) per disease	*P*-value death	Septicemic foals % (N) per disease	Death % of septicemic foals (N)
Critically ill	95.0 (211)	34.6 (73/211)	.21	46.4 (98/211)	44.9 (44/98)
Sepsis	43.9 (98)	44.9 (44/98)	.009		
NMS	8.6 (19)	26.3 (5/19)	.28	31.6 (6/19)	50.0 (3/6)
PA	5.4 (12)	8.3 (1/12)	.10	8.3 (1/12)	0.0 (0)
Enteritis	14.0 (31)	19.4 (6/31)	.06	48.4 (15/31)	33.3 (5/15)
Pneumonia	4.5 (10)	40.0 (4/10)	.52	60.0 (6/10)	50.0 (3/6)
Omphalitis	9.0 (20)	35.0 (7/20)	.75	35.0 (7/20)	71.4 (5/7)
Neonatal isoerythrolysis	5.0 (11)	54.5 (6/11)	.17	27.3 (3/11)	66.6 (2/3)
Bladder rupture	1.8 (4)	25.0 (1/4)	.68	25.0 (1/4)	100.0 (1/1)
FTP	31.5 (70)	48.6 (34/70)	<.001	60.0 (42/70)	57.1 (24/42)
Other diseases	5.0 (12)	33.3 (4/12)	.75	0.0 (0)	0.0 (0)

Abbreviations: FTP, failure of transfer of passive immunity; N, number of foals; NMS, neonatal maladjustment syndrome; PA, polyarthritis.

TABLE 3 Results of univariable Cox survival analysis of factors associated with death in 222 hospitalized foals aged ≤7 days upon admission.

Variable	Categories	Observed death % (n/N)	HR	95% CI	*P*-value
Breed	Other (ref)	37.0 (10/27)			**.02**
	Warmblood	28.6 (38/133)	0.76	0.38-1.5	.43
	Draft Horse	63.6 (7/11)	2.5	0.95-6.8	.06
Sex	Male (ref)	32.5 (37/114)			
	Female	36.1 (35/97)	1.0	0.65-1.6	.91
Weight (kg)	≥53.0 (ref)	28.6 (24/84)			
	<53.0	38.7 (46/119)	1.3	0.82-2.2	.24
Age (days)	≥3.0 (ref)	24.1 (13/54)			
	<3.0	37.4 (61/163)	1.5	0.83-2.8	.18
Temperature (°C)	≥37.0 (ref)	32.6 (59/181)			
	<37.0	59.1 (13/22)	2.0	1.1-3.7	**.02**
Heart rate (bpm)	≤90.0 (ref)	31.0 (18/58)			
	>90.0	34.9 (52/149)	1.1	0.63-1.8	.80
Pulse strength	Normal (ref)	31.0 (39/126)			
	Abnormal	41.2 (7/17)	1.4	0.63-3.2	.39
Heart murmur (systolic murmur)	Absent (ref)	35.4 (69/195)			
	Present	19.2 (5/26)	0.53	0.21-1.3	.16
Lung auscultation	Normal (ref)	33.3 (66/198)			
	Abnormal	100.0 (3/3)	5.8	1.8-18.8	**.003**
Dyspnea	Absent (ref)	26.5 (30/113)			
	Present	52.8 (19/36)	2.6	1.5-4.7	**.001**
Respiratory rate (/min)	≤50.0 (ref)	33.1 (43/130)			
	>50.0	36.8 (25/68)	1.3	0.77-2.1	.36
Comatose mental state	Absent (ref)	29.7 (46/155)			
	Present	80.0 (12/15)	3.6	1.9-6.8	**<.001**
Recumbency (lateral/sternal)	Absent (ref)	20.7 (17/82)			
	Present	47.9 (35/73)	2.6	1.5-4.6	**.001**
Mucosal membrane color (abnormal)	Normal (ref)	21.9 (23/105)			
	Abnormal	47.5 (47/99)	2.6	1.6-4.3	**<.001**
Capillary refill time (seconds)	<2 (ref)	22.8 (21/92)			
	≥2	49.4 (38/77)	2.6	1.5-4.4	**<.001**
Enteritis	Absent (ref)	35.7 (25/70)			
	Present	19.4 (6/31)	0.43	0.17-1.0	.06
Pneumonia	Absent (ref)	30.1 (28/93)			
	Present	25.0 (2/8)	1.4	0.50-3.9	.52
Prematurity	Not premature (ref)	37.9 (44/116)			
	Premature	34.0 (17/50)	0.73	0.41-1.3	.27
Antimicrobial use prior to sampling/admission	Not administered (ref)	35.4 (64/181)			
	Administered	25.6 (10/39)	0.74	0.38-1.4	.37
Omphalitis	Absent (ref)	33.3 (67/201)			
	Present	35.0 (7/20)	1.1	0.52-2.5	.75
Suckle reflex	Normal (ref)	12.0 (9/75)			
	Abnormal	46.3 (31/67)	4.2	2.0-8.9	**<.001**
pH	7.4-7.5 (ref)	24.4 (22/90)			**.003**
	<7.4 (1)	49.3 (33/67)	2.3	1.3-3.9	**.003**
	>7.5 (2)	21.4 (6/28)	0.82	0.33-2.0	.67

(Continues)

TABLE 3 (Continued)

Variable	Categories	Observed death % (n/N)	HR	95% CI	*P*-value
Venous pCO_2 (mmHg)	≤45.3 (ref)	26.5 (30/113)			
	>45.3	46.9 (30/64)	1.9	1.1-3.1	**.02**
Venous PO_2 (mmHg)	≤20.3 (ref)	20.0 (1/5)			
	>20.3	33.6 (51/152)	2.3	0.31-16.3	.42
Bicarbonate (HCO_3^-; mEq/L)	≤19.9 (ref)	48.6 (17/35)			**.03**
	19.9 < HCO_3^- ≤ 24.0	21.4 (9/42)	0.34	0.15-0.76	**.009**
	24.0 < HCO_3^- ≤ 27.1	36.7 (18/49)	0.59	0.31-1.2	.13
	27.1 < HCO_3^- ≤ 34.8	25.5 (12/47)	0.42	0.20-0.89	**.02**
PCV (%)	≤48.5 (ref)	29.9 (56/187)			
	>48.5	65.2 (15/23)	2.9	1.6-5.2	**<.001**
Base excess (mEq/L)	−5 ≤ BE ≤ +5 (ref)	30.5 (40/131)			**.003**
	<−5	51.2 (22/43)	2.1	1.2-3.5	**.007**
	>+5	13.0 (3/23)	0.37	0.11-1.2	.10
Blood glucose concentration (mg/dL)	≥76.0 (ref)	28.5 (43/151)			
	<76.0	51.2 (21/41)	2.4	1.4-4.1	**<.001**
Sodium (mEq/L)	<139.1 (ref)	27.5 (38/138)			
	≥139.1	50.0 (25/50)	2.8	1.7-4.7	**<.001**
Potassium (mEq/L)	≤4.5 (ref)	31.0 (53/171)			
	>4.5	43.5 (20/46)	1.6	0.93-2.6	.09
Ionized calcium (mg/dL)	≤1.6 (ref)	43.5 (52/167)			
	>1.6	52.2 (12/23)	1.6	0.89-3.0	.14
Chloride (mEq/L)	<98.5 (ref)	29.4 (25/85)			
	≥98.5	36.2 (34/94)	1.5	0.87-2.5	.15
L-lactate (mg/L)	<373.8 (ref) (<4.2 mmol/L)	19.0 (16/84)			
	≥373.8 (≥4.2 mmol/L)	50.0 (43/86)	3.2	1.8-5.7	**<.001**
BUN (mg/dL)	≤38.6 (ref)	34.4 (62/180)			
	>38.6	46.7 (7/15)	1.4	0.64-3.1	.39
Creatinine (mg/L)	≤1.5 (ref)	27.4 (29/106)			
	>1.5	46.7 (39/82)	1.7	1.1-2.8	**.02**
Leukocyte count (10^9/L)	4.9-13.6 (ref)	25.5 (25/98)			**.001**
	<4.9	50.0 (43/86)	2.4	1.5-4.0	**<.001**
	>13.6	25.0 (6/24)	1.0	0.42-2.5	.95
Neutrophil count (10^9/L)	2.5-6.9 (ref)	18.2 (6/33)			**.008**
	<2.5	50.0 (16/32)	3.3	1.3-8.4	**.01**
	>6.9	18.5 (5/27)	0.95	0.29-3.1	.93
Neutrophils (%)	55.0-70.0 (ref)	40.6 (13/32)			**.005**
	<55.0	50.0 (34/68)	1.6	0.84-3.0	.15
	>70.0	25.3 (19/75)	0.63	0.31-1.3	.21
Lymphocyte count (10^9/L)	≤1.91 (ref)	28.8 (15/52)			
	>1.91	30.0 (12/40)	0.91	0.38-2.2	.83
Lymphocytes (%)	30.0-45.0 (ref)	43.8 (14/32)			**<.001**
	<30.0	28.0 (28/100)	0.63	0.33-1.2	.17
	>45.0	57.5 (23/40)	2.0	1.0-3.9	.05
Thrombocytes (K/μL)	100-250 (ref)	33.1 (43/130)			**.006**
	<100	61.9 (13/21)	2.5	1.3-4.7	**.004**
	>250	13.1 (11/84)	0.79	0.41-1.5	.49

TABLE 3 (Continued)

Variable	Categories	Observed death % (n/N)	HR	95% CI	*P*-value
Serum amyloid A (μg/mL)	<2054.0 (ref)	21.5 (26/121)			
	≥2054.0	61.5 (8/13)	3.1	1.4-7.0	**.005**
Immunoglobulin G (g/L)	≥8.0 (ref)	23.5 (23/98)			
	<8.0	48.6 (34/70)	2.5	1.5-4.2	**<.001**
Total protein (g/dL)	≤34.5 (ref)	25.0 (3/12)			
	>34.5	36.8 (60/163)	1.5	0.48-4.9	.48
Albumin (g/L)	≤24.5 (ref)	34.7 (33/95)			
	>24.5	41.5 (17/41)	1.4	0.77-2.5	.28
Total bilirubin (mg/L)	≤49.4 (ref)	23.6 (13/55)			
	>49.4	57.1 (24/42)	2.7	1.4-5.4	**.003**
Gamma-glutamyltransferase (U/L)	≤26.5 (ref)	41.7 (5/12)			
	>26.5	50.0 (4/8)	1.8	0.45-7.4	.41
Sepsis	Blood culture negative + CI (ref)	25.0 (31/124)			
	Blood culture positive + CI	44.9 (44/98)	1.9	1.2-3.0	**.009**
Blood culture	Negative (ref)	24.8 (29/117)			
	Positive	43.6 (44/101)	1.9	1.2-3.0	**.009**

Note: Bolded *P*-values are associated with death.

Abbreviations: 95% CI, 95% confidence interval; BUN, blood urea nitrogen; CI, critically ill; HR, hazard ratio; n, deceased foals; N, number of foals; PCV, packed cell volume.

The mean ± SD and median body weight were 48.8 kg ± 14.2 and 50.0 kg (R, 5.0-90.0 kg).

3.2 | Morbidity and death

In Table 2, an overview of the prevalence and associated risk of death of the different diseases affecting neonatal foals is displayed. It is possible that diseases occurred in combination with each other. In the study sample, 95.0% (211/222) were considered critically ill. Sepsis, enteritis, omphalitis, and neonatal maladjustment syndrome (NMS) or perinatal asphyxia syndrome (PAS) were most prevalent. Less prevalent diseases were polyarthritis, neonatal isoerythrolysis, pneumonia, and bladder rupture. The other diseases, as listed in Table 2, were: weakness (n = 4), fever (n = 2), autoimmune hemolytic anemia (n = 1), immune thrombocytopenia (n = 1), trauma (n = 1), premature (n = 1), hepatic encephalopathy (n = 1), and colic (n = 1). The overall case fatality rate was 33.3% (74/222). Risk of death of the critically ill group was 33.6% (71/211). For all neonatal foals, mean ± SD and median survival time were 10.0 days ± 9.7 and 8.0 days (R, 1-62 days). Septic foals (HR = 1.9; 95% CI = 1.2-3.0; *P* = .009) had an increased risk of death. For foals with sepsis, mean ± SD and median survival time were 10.0 days ± 11.3 and 8.0 days (R, 1-60 days). For foals without sepsis, mean ± SD and median survival time were 10.0 days ± 8.3 and 8.0 days (R, 1-62 days).[26]

3.3 | Risk factors for death

Results of the univariable survival analysis are available in Table 3.

The results of the 3 multivariable models are available in Table 4. Kaplan-Meier survival graphs for the 4 frequently used biomarkers, namely L-lactate, SAA, blood glucose concentration, and IgG are given in Figures 1-4.

The decision tree obtained on the training dataset for foals ≤7 days is displayed in Figure 5. Sensitivity and specificity of the tree were respectively 50.9% and 96.4%. Sensitivity dropped to 38.1% and specificity to 86.1% in the validation based on 30% of the dataset (validation tree enclosed in additional files). Accuracy of both training and validation trees were 81.7% and 68.4% respectively.

4 | DISCUSSION

The present study aimed to identify clinical and laboratory risk factors for death, as well as to assess the prevalence and risk of death associated with various diseases in hospitalized foals. The objective was not to develop a predictive model for death but to create an explanatory model to support the future development of survival scoring systems.

A first important observation in this study was the overall case fatality rate of 33.3% (74/222) for hospitalized neonatal foals. This finding falls within the previously reported range of 20%-60% in other studies on hospitalized, critically ill foals.[1-5,12,14-16,18,27] Most prevalent diseases in our study sample were sepsis (43.9%), enteritis (14.0%) and omphalitis (9.0%). A previous study on foals admitted to the intensive care unit with various diseases reported a case fatality rate of 44.9% for sepsis. However, the study did not distinguish between bacteremic and septicemic foals.[14] Survival rates of foals with sepsis vary greatly between 45% and 81%,[4,14,28,29] despite

TABLE 4 Results of the clinical, laboratory, and combined multivariable Cox survival model for factors associated with death in 222 hospitalized foals aged ≤7 days upon admission.

Variable		Category	Death % (n/N)	HR	95% CI	*P*-value	Se % (95% CI)	Sp % (95% CI)	Acc %
Clinical model									
N = 114	Comatose mental state	Absent (ref) Present	23.3% (24/103) 81.8% (9/11)	4.2	1.8-9.8	<.001	27.3 (12.1-42.5)	91.3 (85.1-97.4)	72.6
	Suckle reflex	Present (ref) Weak/absent	12.7% (8/63) 51.0% (26/51)	3.3	1.4-7.7	.006			
Laboratory model									
N = 110	L-Lactate (mg/L)	<373.8 (ref) <4.2 mmol/L ≥373.8 ≥4.2 mmol/L	13.3% (8/60) 42.0% (21/50)	5.1	2.2-11.9	<.001	10.3 (0.7-21.4)	82.5 (74.2-90.8)	63.3
	SAA (μg/mL)	<2054.0 (ref) ≥2054.0	22.4% (22/98) 58.3% (7/12)	4.7	1.9-11.4	<.001			
Combined model									
N = 91	Comatose mental status	Absent (ref) Present	21.4% (18/84) 71.4% (5/7)	2.9	1.1-8.1	.04	13.0 (0.7-26.8)	82.1 (72.9-91.3)	64.4
	L-Lactate (mg/L)	<373.8 (ref) <4.2 mmol/L ≥373.8 ≥4.2 mmol/L	14.0% (7/50) 39.0% (16/41)	4.4	1.7-11.7	.003			
	SAA (μg/mL)	<2054.0 (ref) ≥2054.0	23.2% (19/82) 44.4% (4/9)	3.9	1.2-12.7	.02			

Abbreviations: 95% CI, 95% confidence interval; Acc, accuracy; HR, hazard ratio; n, deceased foals; N, number of foals; SAA, serum amyloid A; Se, sensitivity; Sp, specificity.

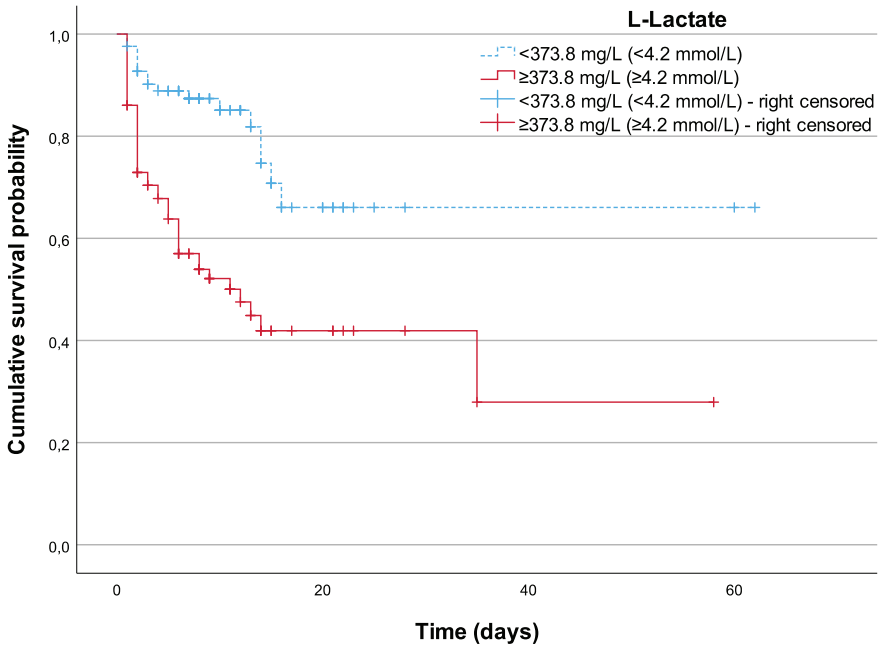

FIGURE 1 Kaplan-Meier graph for survival of hospitalized foals aged ≤7 days stratified by L-lactate (222 cases; HR = 3.2; 95% CI = 1.8-5.7; *P* < .001).

advances in healthcare for these animals.[30] In our study, a foal with sepsis was 1.9 times more likely to die than foals without sepsis. Therefore, sepsis remains an important cause of high morbidity and death in foals, likely because early recognition and appropriate treatment of this disease remains a challenge.[26,31] More diseases in this study with a high risk of death included neonatal isoerythrolysis (54.5%), omphalitis (35.0%), and NMS (26.3%). However, these diseases were not significantly associated with death, possibly due to the limited number of observations. Additionally, not all diseases occurring in our study sample were present alone. Diseases most frequently

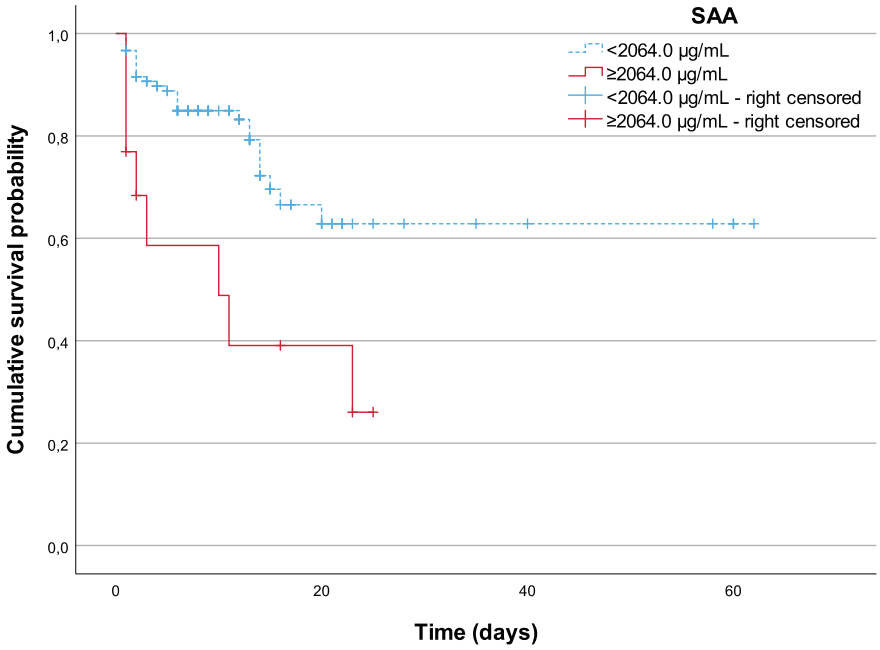

FIGURE 2 Kaplan-Meier graph for survival of hospitalized foals aged ≤7 days stratified by serum amyloid A (SAA; 222 cases; HR = 3.1; 95% CI = 1.4-7.0; $P = .005$).

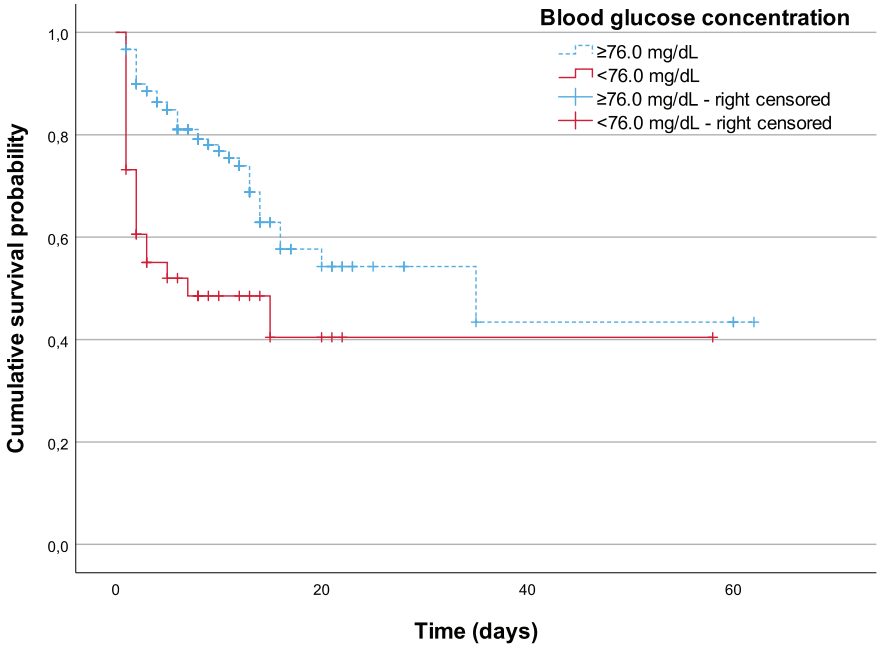

FIGURE 3 Kaplan-Meier graph for survival of hospitalized foals aged ≤7 days stratified by blood glucose concentration (222 cases; HR = 2.4; 95% CI = 1.4-4.1; $P < .001$).

occurring in combination with sepsis were pneumonia, enteritis, and omphalitis. Additionally, failure of transfer of passive immunity (FTP) was frequent in this group of foals, occurring both as an isolated condition (12.6%) as well as in combination with sepsis (18.9%). Risk of death of FTP was higher when sepsis was present (57.1%) compared to when sepsis was absent (35.7%). However, foals without FTP but with sepsis had a risk of death of 31.4%. In other studies, studying healthy and hospitalized foals ≤38 days old, risk of death of FTP was reported between 23.9% and 80.1%.[11,32-36] The second aim of our study was to explore clinical and blood parameters for their relationship with death using Cox survival analysis to better inform owners and veterinarians on the prognosis when hospitalizing a foal. Special interest lies in gaining insight into the diagnostic performance of popular point-of-care tests determining L-lactate, SAA or blood glucose concentration. Previously identified risk factors (comatose mental state, absence of suckle reflex, hypothermia, leukopenia, neutropenia, hypoglycemia, decreased IgG concentrations and increased L-lactate and SAA levels) and a new risk factor (abnormal mucosal membrane color) showing significance in predicting death were found.[4,18,19,21] Risk factors showing significance in predicting death in our multivariable model were comatose mental state, absence of suckle reflex, L-lactate, and SAA. The obtained models exhibited a very low sensitivity and moderate to high specificity. Consequently, the models are prone to generating a significant number of false negatives, indicating

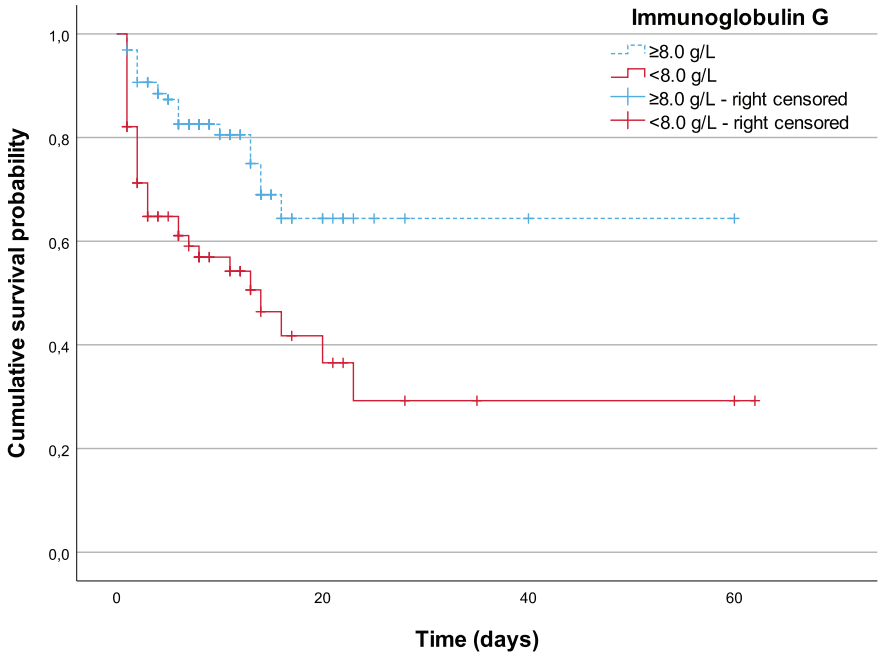

FIGURE 4 Kaplan-Meier graph for survival of hospitalized foals aged ≤7 days stratified by immunoglobulin G (222 cases; HR = 2.6; 95% CI = 1.5-4.5; $P < .001$).

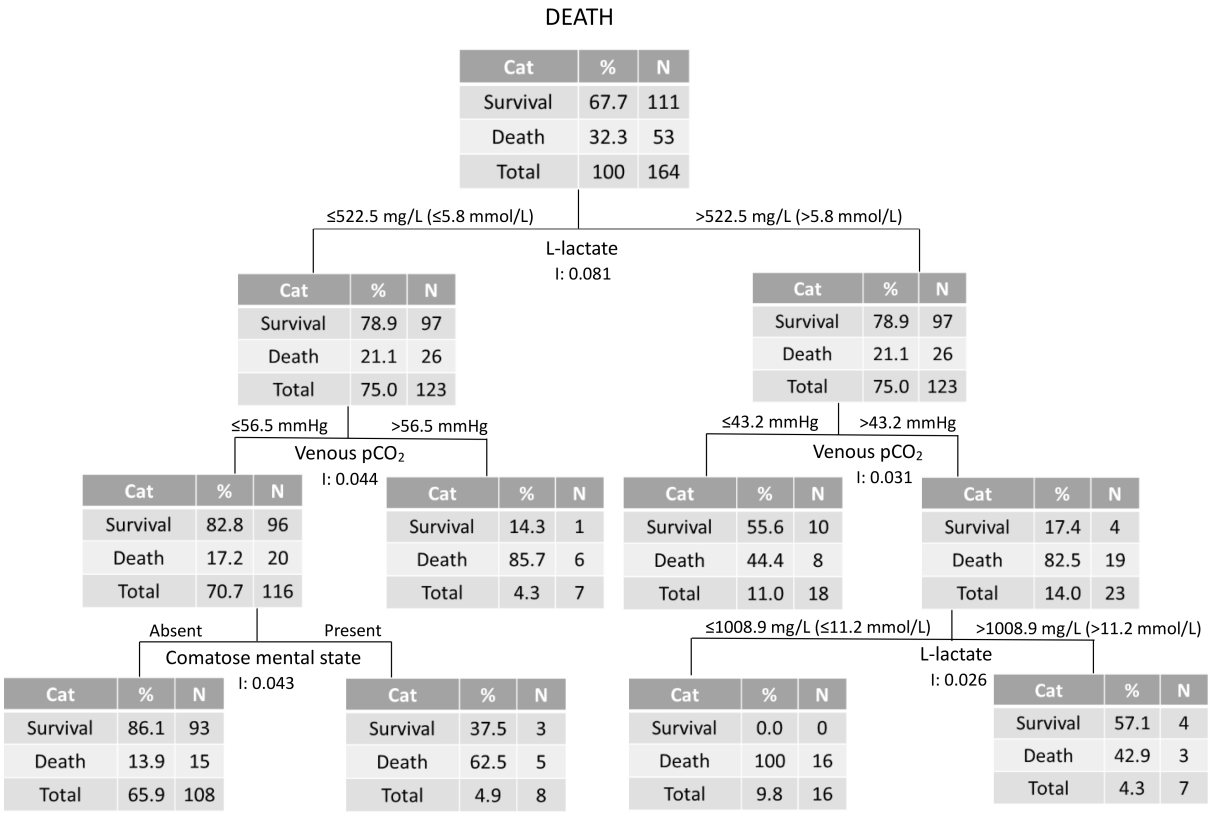

FIGURE 5 Decision tree (training set) for death in 222 hospitalized neonatal foals (≤7 days) based on clinical and laboratory findings (Se = 50.9%; Sp = 96.4%; Acc = 81.7%). Cat, category; I, improvement; N, foals included.

that many foals predicted to survive by the model, might not be in reality. Logically, comatose mental state and suckle reflex are mutually exclusive. In our dataset, no foals were observed to be comatose while retaining a suckling reflex. Therefore, it was not possible to analyze interactions between these variables. Two other studies on hospitalizing foals aged up to 7 and 14 days old, support these findings that the presence of a positive suckle reflex in foals is associated with survival attributable to their non-comatose state.[15,37] Also in the

study of Gayle et al. (1998),[19] a greater percentage of surviving foals exhibited a suckle reflex compared to those that did not, although this difference was not statistically significant. Similarly, a higher percentage of foals that were standing upon admission and thus were in a non-comatose state, demonstrated a suckle reflex. Therefore, it is reasonable that most foals which still possess a suckle reflex remain standing.[19] Furthermore, SAA remained in the combined model for neonatal foals highlighting its predictive value for death in hospitalized foals and therefore demonstrating its utility.[10,38,39] As an acute phase protein, SAA increases rapidly in response to non-specific inflammatory or infectious processes.[10,38,39] Hence, it is fair to say that it has to some extent a value in predicting death. It is important to note that SAA can be stimulated in utero due to an in-utero infection[38] and 72 hours after parturition it can be slightly above the reference range due to a low-grade inflammation associated with parturition.[10,40] In our study, a cut-off value of ≥2054 μg/mL was found to predict death. This cut-off is substantially higher than in a previous study in foals <14 days old (1250 μg/mL). However, the aforementioned study was designed as a multicentric study whereby different methods and machines were used for the analysis of SAA.[10] In the present study, L-lactate was consistently included throughout the different analyses, remaining in both the final combined multivariable model and the decision tree. Increased L-lactatemia indicates hypovolemia and tissue hypoxemia due to hypoperfusion and stimulated anaerobic glycolysis leading to multi-organ dysfunction syndrome (MODS). In humans with suspected infection or sepsis, numerous studies have shown that L-lactatemia above the reference range on admission might prove to be a significant predictor of death.[4,7-9,18,41-44] However, findings across studies were inconsistent and no specific cut-off has been globally established to predict death.[41-44] Therefore, L-lactate concentrations are not recommended as a sole prognostic tool in the intensive care unit. Nonetheless, monitoring L-lactate levels is valuable when integrated into goal-directed (fluid-oxygen) therapy aimed at decreasing L-lactate. Progressive lowering of values reflects a systemic response to fluid therapy, which has a better prognosis in foals.[2,4,8,9] This improved prognosis is also observed in humans.[41-45] Two additional biomarkers, blood glucose concentration and IgG levels, measured via point-of-care tests, along with L-lactate and SAA, were analyzed for their association with death. Both biomarkers demonstrated a statistically significant association with death in the univariable analysis, corroborating findings from previous studies in hospitalized foals.[4,14,16,46,47] Low blood glucose concentrations (<75.0 and <50.0 mg/dL) were identified as a significant risk factor for death in foals in different studies.[3,8,18,46] Hypoglycemia occurs more frequently in foals due to their increased susceptibility caused by low glycogen reserves at birth and tendencies of increased catabolism. However, blood glucose concentration did not feature in our final multivariable model, likely due to its interaction with other, more significant variables. Based on the present study, an association between glucose and death was confirmed, although its value as a single diagnostic test seems insufficient due its low sensitivity. Also, in the present study glucose was measured in laboratory conditions, whereas in practice, handheld glucose meters are popular. These meters are however designed for use in humans and their measurement accuracy is not absolute, as demonstrated in calves.[48] Decreased levels of IgG (<8 g/L) or FTP, are a major risk factor for developing sepsis or other (neonatal) diseases.[1,8,11,18,29,36,37,49,50] In our study, as in calves, an association between FTP and death was present, which is in contrast with previous studies in foals.[13,17,19,36] However, Hurcombe et al. (2008)[3] and Liepman et al. (2015),[11] demonstrated FTP as significantly associated with death.[3,11] The application of the SNAP Foal IgG test has been rigorously evaluated in clinical settings, demonstrating notable sensitivity and specificity when compared to other diagnostic methods such as single radial immunodiffusion, BRIX refractometry, serum glutaraldehyde coagulation test, total globulin calculation, and total protein concentration measurement. The SNAP test exhibits good sensitivity and specificity at both low (<400 mg/dL) and high (>800 mg/dL) IgG concentration ranges. However, its accuracy diminishes for intermediate IgG concentrations (400-800 mg/dL). Despite this, the SNAP Foal IgG test remains sufficiently precise to be a reliable tool for diagnosing FTP.[36,51-53] Further, this study was the first to attempt the use of a CART analysis to predict survival chances of hospitalized sick neonatal foals. Decision trees offer the advantage of being very intuitive to implement in a clinical setting. Multiple decision trees were possible. Selection was made based on clinical relevance, accessibility and objectivity of the variables. Except for venous pCO_2, the same variables were included in the established decision trees, as in the survival analysis. Likely, elevated venous pCO_2 might result from increased CO_2 production in diseased tissues, such as those affected by fever and sepsis, or from reduced ventilation in the foal. This association between increased venous pCO_2 and death has previously been reported in a single study, including foals until 21 days old.[9] In the present study, we attempted to make a validation of the decision tree. It is noteworthy that in the training dataset, L-lactate appears twice on the same side of the decision tree with different cut-off values. Although this might seem counterintuitive, highlighting the complexity of variable interactions. However, this effect is not observed in the validation tree, which was developed using an independent subset of the data. This suggests that the initial finding may be specific to the characteristics of the training set. This underscores the importance of using validation sets to confirm model robustness and to identify any data-specific anomalies. Compared to the survival models, total accuracy was higher, due to a substantially higher sensitivity and only a slightly lower specificity. In the present study, we did not validate the survival models due to the low sample size, however the reader needs to take into account that any validation will likely reduce their sensitivity and specificity.[12] Models with high specificity, such as the survival models in the present study, have few false positives, increasing the certainty around a positive outcome, death in this case. Whether the information would be helpful in decision-making is up to the treating veterinarian to decide, but the authors recommend using the models from the present study with caution.

The present study has several limitations. Although the study, within the field of equine medicine, included a large cohort of hospitalized foals, drawn from a single clinic over an extensive

observational study period, sample size was still limited to build and validate models. Also, the retrospective nature caused incomplete data and missing values. Next to reporting and information bias, also selection bias (no random sample), inter- and intra-observer bias might have occurred. To counter the latter, clinicians were trained by the same senior supervisors and the authors attempted to objectify the factors as much as possible for analysis. Further, the dataset did not allow to make the distinction between natural death and euthanasia on ethical or economic grounds. This uncertainty poses challenges in assessing death percentage and understanding the underlying factors contributing to foal death within veterinary research. Also, regarding the definition of sepsis, some limitations need to be considered. It is challenging to define both a critically ill and septicemic foal because no clear definitions are available in veterinary medicine. In human medicine, sepsis definitions tend to change over the years, ranging from the very wide but inaccurate SIRS to quick Sequential organ failure assessment for which laboratory testing is needed. However, human and veterinary definitions are now dissimilar. A global approach for sepsis is needed for One Health which will aid both researchers and veterinarians to improve patient outcomes. In the near future, a committee of sepsis experts will try to establish a consensus definition and identify predictors of sepsis in veterinary medicine.[44,54-56] However, given the existing ambiguity and the potential to extrapolate underlying mechanisms of sepsis across human and veterinary species, we opted to use a positive blood culture result in a critically ill foal as the definition for sepsis, as was done previously.[57,58] This approach is however limited by the relatively low sensitivity of blood culture and by isolation of possible contaminants causing bloodstream infections but no disease. Therefore, the associations between sepsis and death might have been biased.[50,59-61] This because a positive blood culture remains the reference standard in human medicine to diagnose bloodstream infections.[57] However, blood cultures have low sensitivity, thus false-negative results might have been frequent, potentially due to antimicrobial use before admission. Additionally, false-positive results might have been common due to the risk of contamination.[57] Another limitation is that the design of the present study explored parallel testing strategies for death, meaning measuring all risk factors at the same time. In practice, serial testing, for example first a clinical screening test and subsequently a point-of-care biomarker test, is more frequently done. Serial testing will increase specificity, hence higher confidence in a prediction of death, but our study did not evaluate these serial testing combinations.[17]

In conclusion, this observational study highlighted that sepsis and enteritis remain the most frequently encountered diseases of neonatal hospitalized foals. Only sepsis was associated with death. Survival and CART analysis identified comatose mental state, absence of suckle reflex, elevated L-lactate, SAA and increased venous pCO_2 levels as risk factors for death. The decision tree had a higher diagnostic performance compared to the survival model, but for all models, sensitivity was too low for usage as a decision tool for euthanasia in practice. The same conclusion was drawn for point-of-care testing of L-lactate, SAA, blood glucose concentration and IgG, whereby it was confirmed that currently in use clinical signs and biomarkers are insufficient for providing reliable decision support for euthanasia. Nevertheless, the identified factors might be informative for veterinarians and owners in their decision-making to euthanize for economic or welfare reasons. Therefore, further research should focus on identifying novel biomarkers for this purpose.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. Koterba AM, Brewer BD, Tarplee FA. Clinical and clinicopathological characteristics of the septicaemic neonatal foal: review of 38 cases. *Equine Vet J*. 1984;16(4):376-382. doi:10.1111/j.2042-3306.1984.tb01950.x
2. Corley KTT, Donaldson LL, Furr MO. Arterial lactate concentration, hospital survival, sepsis and SIRS in critically ill neonatal foals. *Equine Vet J*. 2005;37(1):53-59.
3. Hurcombe SDA, Toribio RE, Slovis N, et al. Blood arginine vasopressin, adrenocorticotropin hormone, and cortisol concentrations at admission in septic and critically ill foals and their association with survival. *J Vet Intern Med*. 2008;22(3):639-647.
4. Dembek KA, Hurcombe SD, Frazer ML, Morresey PR, Toribio RE. Development of a likelihood of survival scoring system for hospitalized equine neonates using generalized boosted regression modeling. *PLoS One*. 2014;9(10):e109212.
5. Sanchez C, Giguère S, Lester G. Factors associated with survival of neonatal foals with bacteremia and racing performance of surviving Thoroughbreds: 423 cases (1982–2007). *Am Vet Med Assoc*. 2008;233(9):1446-1452.

6. Castagnetti C, Veronesi MC. Prognostic factors in the sick neonatal foal. *Vet Res Commun*. 2008;32 Suppl 1(SUPPL. 1):87-91.
7. Wong DM, Ruby RE, Dembek KA, et al. Evaluation of updated sepsis scoring systems and systemic inflammatory response syndrome criteria and their association with sepsis in equine neonates. *J Vet Intern Med*. 2018;32(3):1185-1193.
8. Wilkins PA. Prognostic indicators for survival and athletic outcome in critically ill neonatal foals. *Vet Clin North Am Equine Pract*. 2015;31:615-628.
9. Viu J, Armengou L, Ríos J, Cesarini C, Jose-Cunilleras E. Acid base imbalances in ill neonatal foals and their association with survival. *Equine Vet J*. 2017;49(1):51-57.
10. Hoeberg E, Sånge A, Saegerman C, et al. Serum amyloid A as a marker to detect sepsis and predict outcome in hospitalized neonatal foals. *J Vet Intern Med*. 2022;36(6):2245-2253.
11. Liepman RS, Dembek KA, Slovis NM, Reed SM, Toribio RE. Validation of IgG cut-off values and their association with survival in neonatal foals. *Equine Vet J*. 2015;47(5):526-530.
12. Bohlin A, Saegerman C, Hoeberg E, et al. Evaluation of the foal survival score in a Danish-Swedish population of neonatal foals upon hospital admission. *J Vet Intern Med*. 2019;33(3):1507-1513.
13. Hollis AR, Wilkins PA, Palmer JE, Boston RC. Bacteremia in equine neonatal diarrhea: a retrospective study (1990-2007). *J Vet Intern Med*. 2008;22(5):1203-1209.
14. Hoffman AM, Staempfli HR, Willan A. Prognostic variables for survival of neonatal foals under intensive care. *J Vet Intern Med*. 1992;6(2):89-95.
15. Rohrbach BW, Buchanan BR, Drake JM, et al. Use of a multivariable model to estimate the probability of discharge in hospitalized foals that are 7 days of age or less. *J Am Vet Med Assoc*. 2006;228(11):1748-1756.
16. Saulez MN, Gummow B, Slovis M, et al. Admission clinicopathological data, length of stay, cost and mortality in an equine neonatal intensive care unit. *J S Afr Vet Assoc*. 2007;78(3):153-157.
17. Pas ML, Bokma J, Lowie T, Boyen F, Pardon B. Sepsis and survival in critically ill calves: risk factors and antimicrobial use. *J Vet Intern Med*. 2023;37(1):374-389.
18. Bedenice D, Avila B, Paradis MR. Comparative evaluation of clinical findings and prognostic outcome parameters in hospitalized, critically ill neonatal foals and crias. *J Vet Emerg Crit Care*. 2021;31(5):619-628.
19. Gayle JM, Cohen ND, Chaffin MK. Factors associated with survival in septicemic foals: 65 cases (1988–1995). *J Vet Intern Med*. 1998;12(3):140-146.
20. Corley KTT, Pearce G, Magdesian KG, Wilson WD. Bacteraemia in neonatal foals: clinicopathological differences between gram-positive and gram-negative infections, and single organism and mixed infections. *Equine Vet J*. 2007;39(1):84-89.
21. Raisis AL, Hodgson JL, Hodgson DR. Equine neonatal septicaemia: 24 cases. *Aust Vet J*. 1996;73(4):137-140.
22. Palmer J. Update on the management of neonatal sepsis in horses. *Vet Clin North Am Equine Pract*. 2014;30:317-336.
23. Mckenzie HC, Furr MO. Equine neonatal sepsis: the pathophysiology of severe inflammation and infection. *Comp Cont Educ Prac Vet*. 2001;23(7):661-672.
24. Hatz LA, Hartnack S, Kümmerle J, Hässig M, Bettschart-Wolfensberger R. A study of measurement of noninvasive blood pressure with the oscillometric device, Sentinel, in isoflurane-anaesthetized horses. *Vet Anaesth Analg*. 2015;42(4):369-376.
25. Pardon B, Buczinski S, Deprez PR. Accuracy and inter-rater reliability of lung auscultation by bovine practitioners when compared with ultrasonographic findings. *Vet Rec*. 2019;185(4):109.
26. Brewer BD, Koterba AM. Development of a scoring system for the early diagnosis of equine neonatal sepsis. *Equine Vet J*. 1988;20(1):18-22.
27. Furr M, Tinker MK, Edens L. Prognosis for neonatal foals in an intensive care unit. *J Vet Intern Med*. 1997;11(3):183-188.
28. Hytychová T, Bezděková B. Retrospective evaluation of blood culture isolates and sepsis survival rate in foals in The Czech Republic: 50 cases (2011-2013). *J Vet Emerg Crit Care*. 2015;25(5):660-666.
29. Taylor S. A review of equine sepsis. *Equine Vet Educ*. 2015;27(2):109.
30. Marsh P, Palmer J. Bacterial isolates from blood and their susceptibility patterns in critically ill foals 543 cases (1991-1998). *J Am Vet Med Assoc*. 2001;218(10):1608-1610.
31. Wilson D, Madigan J. Comparison of bacteriologic culture of blood and necropsy specimen for determining the cause of foal septicemia 47 cases (1978-1987). *J Am Vet Med Assoc*. 1989;195(12):1759-1763.
32. Elsohaby I, Riley CB, McClure JT. Usefulness of digital and optical refractometers for the diagnosis of failure of transfer of passive immunity in neonatal foals. *Equine Vet J*. 2019;51(4):451-457.
33. Palmisano M, Javsicas L, McNaughten J, Gamsjäger L, Renaud DL, Gomez DE. Effect of plasma transfusion on serum amyloid A concentration in healthy neonatal foals and foals with failure of transfer of passive immunity. *J Vet Intern Med*. 2023;37(2):697-702.
34. Ujvari S, Schwarzwald CC, Fouché N, Howard J, Schoster A. Validation of a point-of-care quantitative equine IgG turbidimetric immunoassay and comparison of IgG concentrations measured with radial immunodiffusion and a point-of-care IgG ELISA. *J Vet Intern Med*. 2017;31(4):1170-1177.
35. Davis DG, Schaefer DMW, Hinchcliff KW, Wellman ML, Willet VE, Fletcher JM. Measurement of serum IgG in foals by radial immunodiffusion and automated turbidimetric immunoassay. *J Vet Intern Med*. 2005;19(1):93-96.
36. Metzger N, Hinchcliff KW, Hardy J, Schwarzwald CC, Wittum T. Usefulness of a commercial equine IgG test and serum protein concentration as indicators of failure of transfer of passive immunity in hospitalized foals. *J Vet Intern Med*. 2006;20(2):382-387.
37. Sobiraj A, Herfen K, Bostedt H. Clinical symptoms and laboratory data in newborn foals with sepsis-a retrospective analysis. *Pferdeheilkunde*. 2001;17(6):673-675.
38. Barr B, Nieman NM. Serum amyloid A as an aid in diagnosing sepsis in equine neonates. *Equine Vet J*. 2022;54(5):922-926.
39. Belgrave R, Dickey M, Arheart K, Cray C. Assessment of serum amyloid A testing of horses and its clinical application in a specialized equine practice. *J Am Vet Med Assoc*. 2013;243:113-119.
40. Duggan V. Serum amyloid A in the neonatal foal: the significance of peri-parturient events. *Vet J*. 2008;176:267-269.
41. Liu G, Lv H, An Y, Wei X, Yi X, Yi H. Early lactate levels for prediction of mortality in patients with sepsis or septic shock: a meta-analysis. *Int J Clin Exp Med*. 2017;10(1):37-47.
42. Morris E, McCartney D, Lasserson D, Van Den Bruel A, Fisher R, Hayward G. Point-of-care lactate testing for sepsis at presentation to health care: a systematic review of patient outcomes. *Br J Gen Pract*. 2017;67(665):e859-e870.
43. Borthwick HA, Brunt LK, Mitchem KL, Chaloner C. Does lactate measurement performed on admission predict clinical outcome on the intensive care unit? A concise systematic review. *Ann Clin Biochem*. 2012;49(4):391-394.
44. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021;47(11):1181-1247.
45. Lee SM, An WS. New clinical criteria for septic shock: serum lactate level as new emerging vital sign. *J Thorac Dis*. 2016;8(7):1388.
46. Hollis AR, Furr MO, Magdesian KG, et al. Blood glucose concentrations in critically ill neonatal foals. *J Vet Intern Med*. 2008;22(5):1223-1227.
47. Castagnetti C, Pirrone A, Mariella J, Mari G. Venous blood lactate evaluation in equine neonatal intensive care. *Theriogenology*. 2010;73(3):343-357.
48. Gerber KL, Freeman KP. ASVCP guidelines: quality assurance for portable blood glucose meter (glucometer) use in veterinary medicine. *Vet Clin Pathol*. 2016;45(1):10-27.

49. Furr M, McKenzie H. Factors associated with the risk of positive blood culture in neonatal foals presented to a referral center (2000-2014). *J Vet Intern Med*. 2020;34(6):2738-2750.
50. Haas SD, Bristol F, Card CE. Risk factors associated with the incidence of foal mortality in an extensively managed mare herd. *Can Vet J*. 1996;37(2):91-95.
51. Pusterla N, Pusterla JB, Spier SJ, Puget B, Watson JL. Evaluation of the SNAP foal IgG test for the semiquantitative measurement of immunoglobin G in foals. *Vet Rec*. 2002;151(9):258-260.
52. Kasap S, Babaeski S, Yildirim KN, Orman A, Temizel EM, Kennerman E. Evaluation of glutaraldehyde coagulation test and colostrum BRIX refractometer compared with SNAP foal IgG test in neonatal foals. *Equine Vet J*. 2023;56:1077-1082.
53. Sievert M, Schuler G, Büttner K, Wehrend A. Comparison of different methods to determine the absorption of colostral IgG in newborn foals. *J Equine Vet Sci*. 2022;114:104008.
54. Levy MM, Fink MP, Marshall JC, et al. SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med*. 2001;2003:1250-1256.
55. Singer M, Clifford D, Seymour C, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016; 315(8):801-810.
56. Cortellini S, DeClue AE, Giunti M, et al. Defining sepsis in small animals. *J Vet Emerg Crit Care*. 2024;34(2):97-109.
57. Lamy B, Dargère S, Arendrup MC, Parienti JJ, Tattevin P. How to optimize the use of blood cultures for the diagnosis of bloodstream infections? A state-of-the art. *Front Microbiol*. 2016;7:697.
58. Delanghe JR, Speeckaert MM. Translational research and biomarkers in neonatal sepsis. *Clinica Chimica Acta*. 2015;451:46-64.
59. Bindi F, Vernaccini M, Bonelli F, Nocera I, Fanelli D, Sgorbini M. Apgar score, clinical, hemato-biochemical, and venous blood gas parameters in a cohort of newborn mule foals: preliminary data. *J Equine Vet Sci*. 2023;1:130.
60. Carr EA. Field triage of the neonatal foal. *Vet Clin North Am Equine Pract*. 2014;30:283-300.
61. Galvin N, Collins D. Perinatal asphyxia syndrome in the foal – review and a case report. *Ir Vet J*. 2004;57(12):707-714.
62. Ostermann M, Sprigings D. The critically ill patient. In: Sprigings D, Chambers JB, eds. *Acute Medicine: A Practical Guide to the Management of Medical Emergencies*. 5th ed. New Jersey, US: Wiley & Sons; 2017:1-8.
63. Toribio RE. Equine neonatal encephalopathy: facts, evidence, and opinions. *Vet Clin North Am Equine Pract*. 2019;35:363-378.

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