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Original article

RETROSPECTIVE ANALYSIS OF MORTALITY PREDICTORS IN DOGS WITH ACUTE RESPIRATORY FAILURE

G. SIMEONOVA & S. KTISTAKIS

Department of Veterinary Surgery, Faculty of Veterinary Medicine,
Trakia University, Stara Zagora, Bulgaria

Summary

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The aim of the present study was to investigate common clinical and laboratory parameters in dogs suffering from acute respiratory failure caused only by respiratory system disorders, using multiple regression analysis, in order to determine early factors with prognostic significance for survival or death, as well as to suggest a simple score system predicting reliably the probability of lethal outcome. The retrospective investigation was based on data from medical records of dogs suffering from acute respiratory failure, admitted to the Small Animal Clinic of Trakia University, Stara Zagora, Bulgaria between 2007 and 2010. Thirty eight animals, fulfilling the inclusion criteria for the study, were divided in two groups: survived and non-survived. Relationship between signalments, clinical, and laboratory variables and outcomes were evaluated by means of logistic regression analysis. Age over 6 years, heart rate (HR) over 160 min^{-1}, weak pulse, capillary refill time (CRT) above 2 s, respiratory rate (RR) above 40 min^{-1}, the presence of parenchymal lung disease, and non-traumatic lesion turned out to be individual mortality predictive factors. The only three predictors of outcome retained by the multivariate logistic regression model in the present work were RR higher than 40 min^{-1}; CRT above 2 s; and weak pulse. According to our scoring system, a total score bellow 8 points predicted survival with sensitivity 100%, specificity 80.77%, and positive and negative predictive values of 70.6% and 100%, respectively. Dogs that received more than 18 points would die (100% specificity) and those with 12 points were considered with 50% chances to survive (sensitivity 66.67%, specificity 92.31%, positive and negative predictive values of 80.0% and 85.7%, respectively). Based on ROC curve analysis this scoring system classified correctly 91.85% of cases with AUC=0.915 (P=0.0001).

Key words: dog, mortality predictors, respiratory failure, scoring system

INTRODUCTION

Respiratory failure is defined as malfunction of the lungs and the chest to supply oxygen from inhaled air to the bloodstream and to eliminate carbon dioxide in opposite direction (Baltopoulos *et al.,* 2004).

Numerous human medicine studies reported very high mortality rates: 37% (Knaus, 1996); 65% (Monchi *et al.*, 1998); 43% (Zambon & Vincent, 2008) among patients suffering from acute respiratory insufficiency despite novel therapeutic approaches. Several score systems assessing the probability of death based on objective data have been proposed in an attempt to select early discriminant prognostic factors. The most commonly used are lung injury score (LIS), organ system failure (OSF), simplified acute physiology score (SAPS), and SAPS II. SAPS-II was the best for prediction of the outcome in mechanically ventilated patients (Monchi *et al.*, 1998).

The human investigations are directed mainly to the acute respiratory distress syndrome (ARDS) developed in conjunction with different systematic disorders, related not only to the respiratory system. The parameters are connected with expensive and invasive means of measuring, such as pulmonary artery cannulation (Herridge *et al.*, 2003). Moreover, respiratory parameters such as tidal volume, peak end expiratory pressure, mean airway pressure, thoracic compliance, arterial pH, PaO_2, $PaCO_2$, PaO_2/FiO_2 ratio of survivors and non-survivors were not significantly different on the first day of admission (Doyle *et al.*, 1995; Monchi *et al.*, 1998).

Similar studies in veterinary patients are very limited (Frevert & Warner, 1992). The attention is directed to the ARDS as it was connected with 100% mortality rate in dogs when recognized (DeClue & Cohn, 2007). Very few reports describe clinical ARDS in veterinary medicine, as diagnostic criteria require arterial gases and pulmonary arterial wedge pressure measurement to exclude cardiogenic pulmonary oedema (Wilkins *et al.*, 2007). Moreover, ARDS referred only to pulmonary injury ignoring the contribution of the pleural space diseases as a very common cause of death. So, our efforts were to investigate common clinical and laboratory parameters in dogs suffering from acute respiratory failure caused by impairment in respiratory system only by means of multiple regression analysis in order to determine early factors with prognostic significance for survival or death.

The purpose of the study was to discriminate between prognostic factors of survival and mortality in dogs with acute respiratory insufficiency based on simple signalment, clinical, and laboratory parameters and to suggest the most appropriate severity score system for the condition.

MATERIALS AND METHODS

Data collection

The investigation was performed in a retrospective manner based on data from medical records of dogs suffering from acute respiratory failure and admitted to the Small Animal Clinic of Trakia University, Stara Zagora, Bulgaria between 2007 and 2010. Thirty eight animals fulfilled the inclusion criteria for the study, i.e. an acute bout of respiratory distress requiring oxygen supplementation with or without mechanical ventilation. Respiratory distress was defined as severe respiratory difficulty – outwardly evident, physically laboured ventilation or respiratory efforts; clinically evident inability to adequately ventilate and/or oxygenate. The exclusion criteria were: airway obstructions because their outcome depends only on the liberation of the airways; cardiac cause of respiratory distress; some previously applied treatment and presence of underlying disease.

Information about dogs' breed, weight, age, sex, body condition, diagnosis, time elapsed from the beginning of clinical signs, evidence of trauma, main clinical and laboratory parameters such as rectal temperature, heart rate (HR), pulse quality, respiratory rate (RR), type of respiratory distress, presence of cough, mucous membrane colour (MMC), capillary refill time (CRT), haemoglobin (Hb), haematocrit (Hcr), red blood cells count (RBC), white blood cells count (WBC), platelet count (PLT), total protein (TP), albumin (Alb), blood urea nitrogen (BUN), creatinine, blood glucose, total bilirubin (Blr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AlPh) were obtained from the individual patient forms. Differences in these parameters were compared between survivors and non-survivors.

Statistical methods

Relationship between signalments, clinical and laboratory parameters and outcomes were evaluated by means of logistic regression analysis with a statistical software package (MedCalc software v. 10.2.0.0, Belgium).

First, differences in the distribution of independent variables between survivors and non-survivors were evaluated. The Mann-Whitney non-parametric test was used to evaluate the difference of means of continuous parameters between survivors and non-survivors. Chi-square analysis was used for categorical variables. As mean values of vital signs expressed as continuous variables are of little clinical value, since high mortality is only observed either above and/or below their normal ranges, continuous variables were converted into categorical and presented as dicho-/trichotomous variables. For example, although there were no differences in the mean body temperatures between those who died and those who survived, low temperature was associated with an increased chance of death in comparison with high or normal values. The presence of cough, trauma, type of distress, body condition, time elapsed from the beginning, MMC, pulse quality, and final diagnosis were presented as dichotomous variables. Appropriate cut-off points for age, HR, RR and CRT were determined by receiver operating characteristic (ROC) and Youden index analysis.

The effects of single risk factors on death were examined further with logistic regression. Odds ratios (ORs), as a quantitative measurement of association between an outcome and a potential risk factor, were calculated for each parameter. Ninety-five percent confidence intervals (CIs) for OR were also calculated.

After performing univariate logistic regression, all variables that showed a statistically significant relationship to the outcome were entered in a stepwise multivariate regression model. The power of the model's predicted values to discriminate between positive and negative outcome is quantified by the area under the ROC (AUC). It is interpreted as the percent of all possible pairs of cases in which the model assigns a higher probability to a correct than to an incorrect case.

Finally, a new respiratory scoring system was developed based on the results from uni- and multivariate analyses. Its predictive value was also presented by the area under the ROC (AUC). Parameters with P value < 0.05 from univariate analyses received a score point 1, assuming that these parameters had the least impact on the survival; those with P value < 0.01 received 2 points, while all the parameters included in the multivariate model of death prediction received 5 points, so that the maximum score was 22.

RESULTS

The commonest breeds presented with acute respiratory insufficiency were mixed hunting dogs (15), followed by Bulgarian Scenthound (6), Pintcher (6), Pekingese (2), Caucasian Shepherd (2), Kurzhaar (1), Cocker spaniel (1), Pit bull (1), Saint Bernard (1), Chi-hua-hua (1), German Shepherd (1), Giant Schnauzer (1). There

Table 1. Descriptive analyses of signalment, clinical and laboratory variables in survived and non-survived dogs with acute respiratory failure, using Mann-Whitney test for continuous and chi-square test for categorical parameters.

Parameter	Survivors		Non-survivors		
	n	median (range) or ratio (%)	n	median (range) or ratio (%)	P value
Signalment					
Sex (male/female)	26	16/10 (62/38)	12	10/2 (83/17)	0.333
Age, years	26	3.75 (0.3-14)	12	7 (0.25-11)	0.269
Body weight, kg	26	8.3 (1.5-27.5)	12	12.5 (2.2-56)	0.017
Body condition (good/ poor)	26	15/11 (58/42)	12	5/7 (42/58)	0.210
Clinical variables					
Rectal temperature, °C	26	38.7 (36.6–39.7)	12	38.5 (31.0-39.7)	0.190
Rectal temperature (normal, high, low)	26	18/6/2 (69/23/8)	12	5/4/3 (42/33/25)	0.072
Heart rate, min^{-1}	26	140 (88-200)	12	169 (130-220)	0.004
Pulse quality (strong, weak)	26	19/7 (73/27)	12	3/9 (25/75)	0.014
Respiratory rate (RR), min^{-1}	26	45 (16-108)	12	58 (40-120)	0.049
Mucous membrane colour (normal, abnormal)	26	16/10 (62/38)	12	4/8 (33/67)	0.2044
Capillary refill time (CRT) (< 2s; > 2s)	26	22/4 (85/15)	12	3/9 (25/75)	0.0012
Presence of cough (yes, no)	26	19/7 (73/27)	12	8/4 (67/33)	0.9838
Evidence of trauma (yes, no)	26	21/5 (81/19)	12	4/8 (33/67)	0.0125
Distress (expiratory/mixed)	26	21/5 (81/19)	12	9/3 (75/25)	0.8368
Disease (parenchymal/pleural)	26	5/21 (19/81)	12	8/4 (67/33)	0.0376
Time elapsed from the beginning (< 24 hours/ > 24 h)	26	12/14 (46/54)	12	2/10 (17/83)	0.1646
Laboratory variables					
Haemoglobin (Hb), g/l	26	102.5 (71-157)	12	106.5 (82-141)	0.89
Haematocrit (Hcr), l/l	26	0.3 (0.2-0.45)	12	0.31 (0.23-0.39)	0.88
Red blood cells (RBC), T/L	26	5.6 (4.21-9.18)	12	5.41 (3.58-7.89)	0.78
White blood cells (WBC), G/L	26	25.4 (5.9-42.9)	12	16.3 (7.5-55.1)	0.74
Platelets (PLT), G/L	26	147 (41-340)	12	229 (140-312)	0.46
Total protein (TP), g/L	26	62 (45-71)	12	56 (43-81)	0.81
Albumin, g/L	26	26 (18-35)	12	23 (17-38)	0.67
Blood urea nitrogen, mmol/L	26	8.2 (2.9-29.1)	12	5.1 (2.9-13.2)	0.40
Creatinine, µmol/L	26	105.7 (45.0-366.8)	12	100.4(54.4-127.7)	0.27
Glucose, mmol/L	26	6.21 (3.20-9.25)	12	5.96 (4.73-6.9)	0.78
AlPh, U/L	26	98 (25-310)	12	96 (16-270)	0.91
Alanine aminotransferase, U/L	26	89 (50-686)	12	76 (44-145)	0.31
Aspartate aminotransferase, U/L	26	86 (61-556)	12	66 (56-370)	0.69

Table 2. Results of univariate logistic regression analysis showing individual predictors of death in dogs with acute respiratory failure (n=38)

Parameter		n	Odds ratio (OR)	OR (95% confidence interval)	P
Signalment					
Age	< 6 years	25	–		
	> 6 years	13	4.67	1.08–20.2	0.039
Disease	Parenchymal	13	8.00	1.70–37.67	0.0085
	Pleural	25	–		
Clinical parameters					
HR	< 160 min^{-1}	26	–		
	> 160 min^{-1}	12	11.00	2.21–54.75	0.0034
Pulse quality	Strong	22	–		
	Weak	16	8.14	1.70–39.06	0.0087
RR	< 40 min^{-1}	13	0.11	0.01–0.95	0.044
	> 40 min^{-1}	25	–		
CRT	< 2 s	25	–		
	> 2 s	13	16.5	3.06–89.06	0.0011
Trauma	Yes	25	–		
	No	13	8.4	1.79–39.44	0.007

Cut-off points as established by ROC curve analysis: for age: > 6 years (AUC = 0.610); for HR: > 160 min^{-1} (AUC = 0.626); for RR: < 40 min^{-1} (AUC = 0.658); for CRT: > 2 s (AUC = 0.773).

were no differences between survived and non-survived dogs with regard to breed, sex, and body condition but there was difference in body weight between the two groups. The descriptive analysis of the investigated parameters is summarised in Table 1.

According to the univariable logistic regression analysis, presented in Table 2, the following parameters were found to be significantly associated with mortality: age over 6 years, HR over 160 min^{-1}, weak pulse quality, and CRT above 2 s. RR bellow 40 min^{-1} was considered as a negative individual predictor of death as it decreased 10 times the chance for lethal outcome (P=0.0044). The distribution of diseases between live and dead animals differed significantly as animals suffering from parenchymal lung disease had 8 times higher chance to die than animals with occupying pleural space disease (P=0.0085). Furthermore, lethal outcome increased 8.4 times if lung injury was not related to trauma (P=0.007). We did not find any connection between the times elapsed from the beginning of respiratory distress and the outcome. The same was valid for all the investigated laboratory parameters.

The results of multiple regression model with odds ratio for mortality are shown in Table 3. The only three predictors of outcome retained by the multivariable logistic regression model in the present work were RR higher than 40 min^{-1}; CRT above 2 s; and weak pulse quality. The ROC curve analysis of death probabilities predicted by the model showed that 84.21% of cases were correctly classified with AUC=0.928.

Table 3. Individual predictors of death in dogs with acute respiratory failure (n=38) that have entered the multivariate logistic regression model

Variable	Coefficient	Standard error	OR (95% confidence interval)	P value
Constant: –2.1279				
RR below 40 min^{-1}	–3.0950	1.4616	0.04 (0.003–0.80)	0.034
CTR over 2s	2.5147	1.0568	12.36 (1.56–98.11)	0.017
Weak pulse quality	1.8465	1.0673	6.34 (0.78–51.34)	0.081

Table 4. Scoring system used for prediction of death in acute respiratory failure in dogs. Single predictive variables with P value < 0.05 received 1 point; those with P<0.01 received 2 points; and all the parameters entering the multivariate model received 5 points

Parameter	Points
Age over 6 years	1
Non-traumatic injury	2
HR > 160 min^{-1}	2
Parenchyma of the lung affected	2
CRT > 2 s	5
Weak pulse	5
RR > 40 min^{-1}	5
Total maximum score	22

Finally, based on the results, a simple scoring system (Table 4) for prediction of the outcome was composed. According to ROC curve analysis this scoring system classified correctly 91.85% of cases with AUC = 0.915 (P=0.0001). In concordance with our scoring system, a total score < 8 points predicted survival with sensitivity 100%, specificity 80.77%, and positive and negative predictive values of 70.6% and 100%, respectively (Table 5). Animals that received between 8 and 11 points would rather live than die whereas animals with 13 to 16 points would rather die than live. Dogs that received over 18 points will die with 100% specificity and those having 12 points are considered with 50% chances to survive (sensitivity 66.67%, specificity 92.31%, positive and negative predictive values of 80.0% and 85.7%, respectively).

DISCUSSION

The study demonstrates that several simple clinical parameters could be used to assess reliably the probability of bad or benign outcome in dogs with acute respiratory failure. Breed, sex, body condition did not show any connection with the outcome. Although there was a statistically significant difference in body weight between survivors and non-survivors, this parameter was excluded by the model as a single predictive factor.

Our results demonstrated also that there were not any relationships between the outcome and the rectal temperature; MMC; the presence of cough; type of distress; time elapsed from the beginning of laboured breathing; and each of the laboratory parameters.

Significant influence on mortality had age; parenchymal lung injury; elevated HR, RR, and CRT; weak pulse; and non-traumatic cause of respiratory insufficiency.

Accurate predictors of death in dogs with respiratory failure due to disturbance in respiratory system on its own have not been established till now. Most of the in-

Table 5. Criterion values and coordinates of the ROC curve. Test characteristics of the scoring system for different cut-off points in the predicted probability of death

Criterion*	Sensitivity	Specificity	+ LR	– LR	+ PV	– PV
≥ 1	100.00	0.00	1.00		31.6	
>8	100.00	80.77	5.20	0.00	70.6	100.0
>11	91.67	80.77	4.77	0.10	68.7	95.5
>12	*66.67*	*92.31*	*8.67*	*0.36*	*80.0*	*85.7*
>13	41.67	92.31	5.42	0.63	71.4	77.4
>18	0.00	100.00		1.00		68.4

*1–8 points – 100% live; 9–11 points – rather live than dead; 12 points – 50% chance for life; 13–18 points – rather dead than live; > 18 points – 100% dead. LR: likelihood ratio; PV: predictive value

vestigations in this direction were in human patients with ARDS derived from any body system failure and several individual predictors of death were identified.

According to Monchi *et al.* (1998) the triggering risk factor, long period of mechanical ventilation, right ventricular dysfunction, and the oxygenation index were of prognostic value. In another study in humans (Ahmed *et al.*, 2010) advanced age (over 85 years) was a significant independent predictor of in-hospital mortality. The strong relation of mortality with advanced age was confirmed by other investigators (Rocco *et al.*, 2001) and was found in our study as well. The adverse effect of age may be related to underlying health status. In our study we can reject the presense of concurrent diseases to be the cause of age-related mortality, as we excluded the presence of underlying disease during case selection and we did not find significant changes in kindey or liver functions by blood parameters. We suggest that decreased elasticity, diminished regenerative properties and increase fibrous tissue in the lung occuring with age may be connected with increased mortality in aged animals.

Indices of oxygenation and ventilation, including the PaO_2/FIO_2 ratio, do not predict the outcome or risk of death (Davis *et al.*, 1993). The severity of hypoxaemia at the time of diagnosis did not correlate well with survival rates (Peters *et al.*, 1998) while other authors claimed that oxygenation index showed a direct correlation to outcome in a time-independent manner (Trachsel *et al.*, 2005). Additionally, the failure of pulmonary function to improve in the first week of treatment is a poor prognostic factor. So the potential of the lung to return to normal function was more critical than the degree of hypoxygenation. Therefore, ventilation parameters are not the most accurate to determine prognosis early in the development of respiratory failure. Severity of lung injury at the time of entry into the hospital was a major prognostic factor in the study of Vasilyev *et al.* (1995). We used clinical measurements of oxygenation and perfusion such as RR, CRT, HR, and pulse quality and found out that these parameters had the most significant prognostic meaning in respiratory failure. Based on these results might be concluded that the chances for lethal outcome increased dramatically when concurrent cardiovascular impairment occurs.

Similar to the results in our study, the reported mortality of medical patients was much higher than of surgical or trauma patients (Doyle *et al.*, 1995; Milberg *et* *al.*, 1995). This was connected with parenchymal pulmonary disfunction typically treated medically, rather than pleural space disorders, typically treated surgically. Knaus *et al.* (1994) also found that surgical patients, i.e., patients with indirect lung injury, had a higher survival rate than patients with medical diagnoses.

Other investigators studied the role of more sophisticated measurements to determine the prognosis. Peripheral blood levels of decoy receptor 3 (DcR3), a soluble protein with immunomodulatory effects, independently predicted 28-day mortality in ARDS patients. In a study comparing DcR3, soluble triggering receptor expressed on myeloid cells (sTREM)-1, TNF-alpha, and IL-6 in ARDS patients, plasma DcR3 levels were the only biomarker to distinguish survivors from nonsurvivors at all time points in week 1 of ARDS. Nonsurvivors had higher DcR3 levels than survivors, regardless of APACHE II scores, and mortality was higher in patients with higher DcR3 levels (Chen *et al.*, 2009).

Most of the deaths in ARDS are attributable to sepsis or multiorgan failure rather than a primary pulmonary cause. So prognosis in ARDS patients could not be accepted fully in patients with respiratory failure due to respiratory system disorder alone.

Several score systems were used to assess the severity and to predict mortality in acute respiratory failure. Each of them had different prognostic value.

Lung injury score (LIS) was created on the base of four criteria: chest radiography score for alveolar consolidation, hypoxaemia score (PaO2/FiO2), respiratory compliance score when ventilated, and positive end-expiratory pressure score when ventilated (Murray *et al.*, 1988). This score system can be used to define acute lung injury (ALI) but not to predict mortality in respiratory insufficiency. Gundre *et al.* (2009) evaluated the usefulness of Murray's score in predicting successful extubation in patients with respiratory failure and concluded that patients with Murray's score more than 2 could not be extubated and this correlated to the severity of lung injury. This score system assessed only the severity of pulmonary disfunction but did not make any relation to the mortality. Moreover, it was based on several ventilatory parameters while our aim was to create a scoring system with simple clinical and laboratory parameters which could reliably predict mortality.

Rocco *et al.* (2001) identified seven predictor variables that met entry criteria into the multiple logistic model to predict death: gender, age, peak airway pressure, mean airway pressure, multiple organ disfunction score (MODS), LIS, and ARDS score. MODS evaluates simple physiologic measurements of disfunction in six organ systems. Although having some predictive value, the MODS score is not specific to the respiratory system only. ARDS score is calculated similarly to LIS and takes into account five ctiteria – four are the same as LIS and the fifth is minute ventilation. MODS, LIS and ARDS scores have the same significance as independant prognostic factors for death. The age over 75 years was the strongest predictor of death as it increases the chance for fatal outcome 15 times. Patients with combination of negative predictors such as advanced age, MODS over 8 points, and LIS more than 3 points had 97% probability of death. Hence, multivariate analysis should be used to predict outcome because several factors have mutual and combined influence upon survival.

Our scoring system is simple, could be used in daily veterinary practice, and is reliable in predicting death from respiratory failure that resulted from disturbance in the respiratory system only. Three parameters had the most significant prognostic value: increased CRT, weak pulse, and RR above 40 min^{-1}. According to our score system, 12 points was the threshold for 50% chance to survive with sensitivity 66.63% and specificity 92.31%. Death probability was 100% when the patient score exceeded 18 points and null when the score was 8 points.

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Correspondence:

Assoc. Prof. Galina Simeonova PhD
Department of Veterinary Surgery,
Faculty of Veterinary Medicine
6000 Stara Zagora, Bulgaria,
e-mail: galinavet@abv.bg