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Zero-inflated models for identifying disease risk factors when case detection is imperfect: Application to highly pathogenic avian influenza H5N1 in Thailand

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1 Negative-pressure pulmonary edema in 35 dogs

2

3 Abstract

4 Objective: To describe the clinical characteristics and outcomes in a population
5 of dogs with negative-pressure pulmonary edema (NPPE) and to identify the
6 main causes of the disease. To evaluate any associations with morbidity and
7 mortality.

8 Design: Retrospective study.

9 Setting: Three university teaching hospitals and two private referral centers.

10 Animals: Thirty-five client-owned dogs presented with NPPE.

11 Interventions: None

12 Measurements and Main Results: Data collected included patient characteristics,
13 clinical history, clinicopathological abnormalities, radiographic features,
14 treatments and outcome. Median age was 4 months (range 2-90) and median
15 weight was 7.1 kg (range 1.7-37.2). There were many causes of NPPE including
16 leash tugs, near hanging, accidental choking, anatomical obstruction to airflow
17 and purposeful airway obstruction by people. The most common cause of NPPE
18 was accidental choking (40% of cases). Dogs with an anatomical obstruction
19 were older than 24 months. Hypoxemia with an increased alveolar-arterial
20 gradient was common on presentation. The majority of thoracic radiographs
21 (65.7%) showed an alveolar or interstitial pattern in the caudodorsal area as
22 previously described in the literature. Oxygen therapy was administered to 33
23 (94.3%) dogs. Furosemide was administered to 18 (51.4%) dogs. Median length
24 of hospitalization was 2 days (range 0-14). Twenty-eight (80%) dogs survived to
25 discharge. Seven dogs were mechanically ventilated and only 2 of them (28.6%)

26 survived to discharge. Requirement for mechanical ventilation ($p < 0.001$) was the
27 only parameter associated with mortality.

28 Conclusions: Most cases of NPPE occur in juvenile dogs. Different incidents
29 associated with upper airway obstruction can produce an episode of NPPE.
30 Choking on food or toys and near hanging have not been previously described in
31 the veterinary literature as inciting causes of NPPE. The overall prognosis is
32 good.

33

34 Abbreviation List

35 ARDS: acute respiratory distress syndrome

36 A-a: alveolar-arterial (gradient)

37 BAL: bronchoalveolar lavage

38 BP: blood pressure

39 BOAS: brachycephalic obstructive airway syndrome

40 CT: computed tomography

41 NPPE: negative-pressure pulmonary edema

42 PBF: pulmonary blood flow

43 PE: pulmonary edema

44 SpO₂: blood oxygen saturation measured with pulse oximetry

45 TP: total protein

46

47 Introduction

48 Pulmonary edema (PE) is the accumulation of serous or serohemorrhagic
49 fluid in the pulmonary interstitial space and alveoli. Patients with PE have been
50 traditionally classified as having cardiogenic PE or non-cardiogenic PE.¹ The
51 pathophysiological classification of PE based on changes of the pulmonary
52 parenchyma and pulmonary vasculature differentiates 3 groups of PE: high-
53 pressure PE, increased-permeability PE and mixed-cause PE.² High-pressure PE is
54 due to an increase in pulmonary hydrostatic pressure and is associated with left-
55 sided congestive heart failure and/or overzealous fluid therapy. Increased-
56 permeability PE occurs secondary to damage of the respiratory membrane as seen
57 in acute respiratory distress syndrome (ARDS), pulmonary thromboembolism,
58 ventilator-associated lung injury or inhalation of toxins. Mixed-cause PE is

59 produced by concurrent changes in pulmonary vascular pressures and
60 permeability of the vascular beds. Mixed-cause PE include neurogenic PE
61 (produced by seizures, traumatic brain injury or electrocution), re-expansion PE
62 and negative-pressure PE (NPPE).²

63 NPPE, also called “post-obstructive PE”, occurs due to vigorous inspiratory
64 efforts against an obstructed airway. In human medicine this is known as the
65 Müller maneuver and is used diagnostically in certain settings.³ These efforts
66 produce large negative pleural pressures that increase transvascular fluid
67 filtration and precipitate interstitial and alveolar edema. The pathophysiology of
68 NPPE could be explained by a rise in pulmonary capillary pressure associated with
69 the transient drop in intrathoracic pressure and subsequent increase in venous
70 return to the right side of the heart. In addition, the negative pleural pressure
71 transmits to the pericardium increasing cardiac afterload. The increase in
72 afterload elevates left ventricular, left atrial and hence pulmonary capillary
73 pressures. This upsurge in pressure promotes fluid movement from the
74 pulmonary capillaries towards the pulmonary interstitial space and alveoli.
75 Moreover, nervousness associated with airway obstruction and hypoxemia may
76 produce sympathetic activation contributing towards further increases in cardiac
77 afterload.⁴⁻⁶ In the majority of human patients these mechanisms produce a low-
78 protein edema fluid, demonstrated by a low edema fluid-to-plasma protein ratio
79 (<0.65), although a small subset of patients present with values above this cutoff
80 suggesting an additional increased permeability mechanism. This may be due to
81 pressure-induced rupture of pulmonary capillaries as some patients present with
82 blood-tinged pulmonary secretions.^{5,7}

83 There is a lack of veterinary information relating to this condition and no
84 information from multiple centers. Two veterinary publications have described
85 NPPE in companion animals. One described 9 adult dogs with PE due to
86 anatomical upper airway obstruction including laryngeal paralysis, laryngeal
87 edema, laryngeal polyps and laryngeal fibrosarcoma. All dogs survived to
88 discharge.⁸ The second publication described a population of 26 dogs and cats
89 with non-cardiogenic PE of which 6 dogs and 2 cats had presumed NPPE
90 secondary to airway obstruction. Six of these animals with NPPE were less than 1
91 year old and causes included leash tugs, human physical restraint and
92 brachycephalic obstructive airway syndrome (BOAS). Amongst the cats and dogs
93 with NPPE there was a 50% mortality rate. Six out of 26 patients with non-
94 cardiogenic PE required mechanical ventilation and only 1 of these survived to
95 discharge.⁹

96 The objective of our study is to describe a population of dogs presenting
97 with NPPE to 5 clinics in XXXX. A secondary objective was to evaluate any
98 associations with morbidity and mortality.

99

100 Materials and Methods

101 This study was approved by the primary author's institution's Ethics and
102 Welfare committee (ethics reference number M2016 0080). The databases of 3
103 teaching hospitals and 2 private practices in XXXX were retrospectively searched
104 for dogs with a clinical diagnosis of NPPE presenting between 2006 and 2018.
105 Dogs were included in the study if they had acute signs of tachypnea and/or
106 dyspnea and a clinical history compatible with NPPE. The clinical history was

107 suggestive of NPPE when there was a witnessed or suspected episode of upper
108 respiratory tract obstruction.

109 Data collected included patient demographics, clinical history, admission
110 physical examination findings, blood test results [arterial and venous blood gases,
111 PCV and refractometric total protein (TP), WBC, platelet count, serum
112 biochemistry], blood pressure (systolic Doppler blood pressure or mean
113 oscillometric blood pressure), blood oxygen saturation (SpO₂) with pulse
114 oximetry, thoracic radiographs and computed tomography (CT) scans,
115 echocardiograms, cytological and microbiological results of bronchoalveolar
116 lavage, treatments performed including medications and type of oxygen
117 administration, length of hospitalization and outcome. A board-certified
118 radiologist (XX) reviewed all available radiographs. In patients where arterial
119 blood gas analysis was performed on room air, these results are reported as PaO₂
120 and alveolar-arterial (A-a) gradient. In patients where arterial blood gas analysis
121 was performed on supplemental oxygen, these results are reported as PaO₂/FiO₂
122 ratio. A-a gradients were calculated in patients breathing room air at sea level
123 using the following formula: (A-a) gradient= P_AO₂ - P_aO₂ = [150 - P_aCO₂/0.8] - P_aO₂

124 To further classify the type of upper airway obstruction causing NPPE 5
125 categories were created. Category 1 was injury produced by pulling hard on the
126 dog's leash either by the dog or the dog owner/care giver. Category 2 was an
127 episode of near hanging. Category 3 was choking on foodstuffs or toys. Category 4
128 had an anatomical obstruction to airflow. Category 5 had purposeful airway
129 obstruction by the owner/care giver.

130 Patients that did not survive were categorized into natural death or
131 euthanasia.

132

133 Statistical methods

134 Statistics were performed using a commercial statistical software.^a
135 Normality of the data was assessed using the Shapiro-Wilk test. Continuous
136 parametric data was described as mean and SD and non-parametric data as
137 median and range. A Chi-square test or Fisher's exact test was performed to
138 evaluate the relationship between categorical variables. A Student's t-test was
139 performed to evaluate continuous, normally distributed data and a Mann-Whitney
140 U test for continuous, not normally distributed data. In order to control family-
141 wise error from performing multiple comparisons the Bonferroni correction was
142 applied. After applying the Bonferroni correction, the significance threshold was
143 set at $p < 0.002$.

144 Results

145 Thirty-five cases met the inclusion criteria. There were 19 different breeds
146 represented in the study. Most dogs were crossbreed (6), followed by English
147 Bulldog (4), Cocker Spaniel (3), Labrador Retriever (3) and Staffordshire Bull
148 Terrier (3). Fourteen dogs (40%) were brachycephalic including English bulldog,
149 French bulldog, Staffordshire bull terrier, Chihuahua, pug, Pomeranian, Lhasa
150 Apso and shih tzu. The median age was 4 months (range 2-90) and the median
151 weight was 7.1 kg (range 1.7-37.2). There were 19 entire males (54.3%), 2
152 castrated males (5.7%), 13 entire females (37.1%) and 1 neutered female (2.9%).
153 The majority of cases were referred from a primary care veterinarian (85.7%) and
154 the rest (14.3%) presented as primary care emergencies.

155 There were 10 dogs (28.6%) with NPPE caused by a leash pull (category 1).
156 Six dogs (17.1%) had an episode of near hanging (category 2); two were hanged

157 by their leashes on becoming trapped outside an ascending elevator, one got his
158 head stuck between fencing panels and 3 had a near hanging episode at the
159 groomers' table. Fourteen dogs (40%) had accidental choking (category 3). Nine
160 choked on foodstuffs and 5 choked on toys or balls. There were 3 dogs (8.6%) with
161 an anatomical obstruction to airflow (category 4); one each of laryngeal paralysis,
162 laryngeal collapse and presumed BOAS. All dogs in category 4 were older than 24
163 months of age. Two dogs (5.7%) had purposeful airway obstruction by the
164 owner/care giver (category 5). One dog was restrained round the neck by a dog
165 trainer during a puppy class and the other dog bit its owner whilst playing and in
166 response the owner clamped the muzzle shut while pinning the dog on its back for
167 several seconds.

168 On physical examination 15 (42.9%) dogs were reported as alert, 10
169 (25.7%) were obtunded and one arrived anesthetized to the hospital (2.9%).
170 Mucous membranes were pale in 5 (14.3%), pink in 20 (57.1%), cyanotic in 4
171 (11.4%) and white in 2 (5.7%). The median heart rate was 142 beats per minute
172 (range 56-180), the median respiratory rate 80 breaths per minute (range 20-
173 180) and the median rectal temperature 38.1°C (range 34.9-38.8). Eight dogs
174 were hypothermic on presentation (rectal temperature < 37.9°C) and there were
175 no hyperthermic dogs.

176 Blood pressure (BP) was measured on presentation using the Doppler
177 method in 7 dogs and oscillometric method in 4 dogs. The median Doppler BP was
178 110 mmHg (range 80-120) and the median mean arterial pressure with the
179 oscillometric method was 90 mmHg (range 72-130). Only 2 dogs were classified
180 as hypotensive on presentation (Doppler BP < 100).

181 Pulse oximetry was performed in 15 dogs (42%). Median SpO₂ was 90%
182 (range 56-99). FiO₂ could only be obtained from the medical records from 5 dogs
183 who had pulse oximetry performed; 3 of them were breathing room air and 2 of
184 them were on mechanical ventilation with various FiO₂. One dog had a FiO₂ of 0.6
185 with a SpO₂ of 99% and another dog had a FiO₂ of 1 with a SpO₂ of 91%. Arterial
186 blood gas analysis was performed on 9 patients, 6 of them breathing room air and
187 3 on supplemental oxygen. Patients breathing room air had a low mean PaO₂ [7.5
188 ± 2.5 KPa, RI 10.6-14 (56 ± 19 mmHg, RI 80-105)] with an increased mean (A-a)
189 gradient [6.9 ± 2.4 KPa, RI <2 (52 ± 18 mmHg, RI <15)]. Patients on supplemental
190 oxygen had a low median PaO₂/FiO₂ ratio {10 (10-61) kPa, RI 50.5-66.5 [75 (75-
191 458)]}. Two of these patients had a PaO₂ of 75mmHg with a FiO₂ of 1 and the
192 remaining patient had a PaO₂ of 275mmHg with an FiO₂ of 0.6. The rest of blood
193 test results are displayed in Table 1.

194 Bronchoalveolar lavage (BAL) was performed in 7 (20%) dogs. In 5 dogs
195 BAL was performed soon after commencing mechanical ventilation and one dog
196 after a thoracic CT scan. Cytology in these dogs was consistent with neutrophilic
197 inflammation and microbiological culture was negative. In the remaining dog it
198 was performed 48 hours after commencing mechanical ventilation and cultured
199 *Escherichia coli*, *Enterococcus* spp. and a multi-drug resistant *Pseudomonas*
200 *aeruginosa* due to presumed ventilator-associated pneumonia.

201 Echocardiography was performed in 3 (8.6%) dogs. One dog had reduced
202 systolic function which had resolved 8 days later.

203 Thoracic radiographs were obtained in 32 (91.4%) dogs. One dog had a CT
204 scan only, 3 had CT scan and radiographs and the remaining 2 did not have
205 thoracic imaging due to severe respiratory compromise. Thirty-one radiographic

206 studies were retrieved for review. The pattern of infiltration was defined as
207 alveolar in 26 (74.3%) cases, interstitial to alveolar in 4 (11.4%) cases and purely
208 interstitial in 1 (2.9%) case. The pattern of infiltration was predominantly
209 caudodorsal in 23 (65.7%) cases. All lung lobes were affected in 13 cases (37.1%).
210 The 3 thoracic CT scans documented alveolar patterns in various lung lobes
211 compatible with pulmonary edema.

212 Oxygen therapy was administered to 33 (94.3%) dogs. Two (5.7%) dogs
213 received nasal oxygen through cannulae and 24 (68.6%) dogs via oxygen cages.
214 Seven (20%) dogs had endotracheal intubation and mechanical ventilation. Two
215 (5.7%) dogs had tachypnea and radiographic features of NPPE but improved
216 soon after presentation and did not require oxygen therapy. Antibiotics were
217 administered to 12 (34.2%) dogs. Eight dogs received amoxicillin-clavulanic
218 acid^b and 4 dogs received cefuroxime^c. Eighteen (51.4%) dogs received
219 furosemide^d at any time point. In 10 (28.5%) dogs this was prior to referral and
220 8 (22.9%) dogs at the referral hospital. Median dose of furosemide was 2 mg/kg
221 (range 0.5-6.5).

222 Nine (25.7%) dogs received corticosteroid at any time point.
223 Dexamethasone^e was administered to 5 (14.3%) dogs prior to referral and to 4
224 (11.4%) dogs at the referral hospitals. Median dose of dexamethasone was 0.2
225 mg/kg (range 0.13-0.37).

226 Twenty-eight (80%) dogs survived to discharge. Of the 7 (20%) dogs that
227 did not survive, 4 were euthanized and 3 died naturally. It was not possible to
228 tell from the medical records if euthanasia was financially driven or if it was due
229 to a perceived poor prognosis. Dogs that were mechanically ventilated had a
230 survival rate of 28.6%. Necropsy was performed in 1 non-survivor and identified

231 congested and collapsed lungs consistent with pulmonary edema. The median
232 length of hospitalization was 2 days (range 0-14).

233 Univariate statistical analysis was performed to identify factors that were
234 associated with survival. These results are displayed in tables 2 and 3. PaO₂, A-a
235 gradient, PaO₂/FiO₂ ratio, bicarbonate, BE, total and ionized calcium, albumin,
236 ALT, ALP, total bilirubin, urea and the number of brachycephalic dogs were not
237 included in the analysis as these parameters were only measured in one non-
238 survivor each. Requirement for mechanical ventilation (p<0.001) was the only
239 parameter associated with mortality.

240 Discussion

241 To the authors' knowledge, this is the largest study of dogs with NPPE.
242 The most common incident causing NPPE was choking on foodstuffs or toys
243 (40% of cases). Choking and near hanging had not been previously described as
244 causes of non-cardiogenic PE in veterinary medicine but are well known causes
245 in human medicine, both in infants and adults.¹⁰⁻¹² In order to avoid choking or
246 neck leash injuries in puppies veterinarians may choose to advise their clients to
247 avoid large chews that could block the airway or recommend the use of a body
248 harness instead of a neck collar or neck leash. Although there are a variety of
249 causes producing NPPE we did not find significant differences as regards
250 mortality amongst the different groups.

251 In our study 85% of the cases were less than 1 year old. It is reported that
252 young, healthy people can achieve up to -140 cmH₂O of negative intrathoracic
253 pressure.¹³ It is possible that juvenile dogs, as seen in young humans, can
254 produce larger negative intra-thoracic pressures than adults. Other age-related
255 factors such as the tendency to chew and eat voraciously, tug on the leash and

256 undergo training, may also be a factor. The 3 dogs with an anatomical
257 obstruction to airflow were older than 24 months of age. This is probably
258 because the majority of anatomical obstructions to airflow happen in older dogs,
259 as it is the case of laryngeal paralysis, or develop slowly over the course of
260 months or years, as is the case in BOAS.

261 The majority of thoracic radiographs (65.7% of cases) showed an alveolar
262 or interstitial pattern in the caudodorsal area as previously described in the
263 literature (Figure 1).^{8,9,14} A recent radiographic study found that NPPE produces
264 caudodorsal lung patterns more frequently than the other causes of non-
265 cardiogenic PE.¹⁴ It is unknown why NPPE has this predilection for the
266 caudodorsal area, but it could be that because dogs have increased pulmonary
267 blood volume and flow in the caudal lung lobes¹⁵ they are more likely to have
268 transvascular fluid filtration associated with NPPE in this region. This increase of
269 pulmonary blood flow (PBF) in the dorsocaudal area against gravity is also seen
270 in other standing quadrupeds like horses.¹⁶ Studies of canine PBF under
271 anesthesia and mechanical ventilation show a gravitational effect on PBF^{17,18} as
272 is the case of conscious human subjects¹⁹ but this may not represent what
273 happens in non-anesthetized dogs. Another factor that may play a role in the
274 development of caudodorsal PE is the normal presence of pleural pressure
275 gradients. Dogs have more negative pleural pressures in the dorsal regions of the
276 lung in comparison with the ventral regions.²⁰ In situations of airway obstruction
277 in dogs, pleural pressures may be more negative in the dorsal area hence
278 favouring the development of a caudorsal pattern.

279 Thoracic CT scan was performed in 3 dogs that had thoracic radiography
280 performed. We could not tell from the medical records the indication for this

281 study but one dog had laryngeal paralysis and one dog had laryngeal collapse so
282 a CT might have been performed to rule out concurrent underlying diseases.

283 In human medicine it is common to measure protein concentration of the
284 edema fluid to then calculate the edema fluid-to-plasma protein ratio.²¹ A ratio of
285 <0.65 suggests a low-protein edema as seen in cases of cardiogenic PE but also in
286 the majority of humans with NPPE.⁵ Higher ratios are consistent with increased-
287 permeability PE and mixed-cause PE.²¹ This is uncommonly performed in
288 veterinary medicine and the majority of clinicians perform BAL infusing sterile
289 saline solution into the airway, which would affect the fluid-to-plasma protein
290 ration. The bronchoalveolar fluid obtained in our cases revealed neutrophilic
291 inflammation. This inflammatory response may be due to rupture of pulmonary
292 capillaries resulting from large negative pulmonary pressures.

293 The recommended treatment for NPPE in human medicine is oxygen
294 supplementation and, if necessary, endotracheal intubation and mechanical
295 ventilation with protective ventilation strategies.⁵ Antimicrobials are not
296 indicated, unless there is evidence of additional diseases such as ventilator-
297 associated pneumonia. Furosemide can be considered given that the edema is a
298 low-protein fluid in most cases but there is not strong evidence suggesting its
299 efficacy.⁵ Edema fluid-to-plasma protein ratios have not been measured in
300 veterinary medicine so it is not known whether dogs might benefit from
301 furosemide. Since most events that cause NPPE are transient and there is no
302 persistence of increased pulmonary capillary pressures, furosemide is unlikely to
303 be helpful. The use of furosemide could potentially be deleterious as it may lead
304 to hypovolemia and decreased tissue perfusion. Judicious use of fluid therapy
305 with isotonic crystalloids should be considered to avoid dehydration.

306 Glucocorticoids are not indicated.⁵ They may predispose the patient to
307 gastrointestinal ulceration or increase predisposition to infection among other
308 adverse effects. The administration of corticosteroids or furosemide were not
309 associated with survival in our study, but because of the retrospective
310 observational nature of the study and the small number of dogs that received
311 these drugs, their role in the resolution of the disease cannot be completely
312 excluded.

313 Statistical analysis found that mechanical ventilation requirement was the
314 only parameter associated with mortality. Our study demonstrated an overall
315 survival rate of 80% which is between previous reported values of dogs with
316 NPPE (50% and 100%).^{8,9} The survival rate of dogs requiring mechanical
317 ventilation due to NPPE of our study (28.6%) is lower than the reported survival
318 rates of mechanically ventilated dogs with cardiogenic PE (77%)²² but is higher
319 than the overall canine ARDS population requiring mechanical ventilation (8.3%
320 and 16%).^{23,24} The higher survival rate of ventilated patients with cardiogenic PE
321 compared to NPPE ventilated patients may be related to the effectiveness of
322 diuretic therapy in reducing pulmonary hydrostatic pressure and rapid
323 correction of the underlying mechanism of edema formation in these patients. As
324 patients severely affected by NPPE likely have microvascular permeability
325 alterations and capillary rupture, the edema fluid may be richer in protein and
326 less likely to be eliminated by diuretics.

327

328 Our study has several limitations. Due to its retrospective nature there
329 were some missing data that may have affected our results. Another limitation is
330 the small number of cases. Despite being a multi-institutional study NPPE

331 remains an uncommon cause of PE. Also, because it is an observational study, we
332 cannot draw valid conclusions regarding influence of treatment strategies such
333 as type of oxygen supplementation and use of diuretics. Additionally, we could
334 not ascertain from the medical records whether euthanasia was performed due
335 to a perceived poor prognosis or financial motives and this could have impacted
336 outcome. Another limitation is that by applying the Bonferroni correction a type
337 II statistical error could be committed reducing statistical power.

338

339 In conclusion, most cases of NPPE occur in juvenile dogs. NPPE can
340 happen due to choking on foodstuffs or toys, leash tugs, near hanging, purposeful
341 obstruction by humans or anatomical obstructions. Choking and near hanging
342 have not been previously described in the veterinary literature as inciting causes
343 of NPPE. The overall prognosis is good with a short hospitalization period, unless
344 severe respiratory distress that requires mechanical ventilation ensues.

345

346 Acknowledgments

347

348 Footnotes

- 349 a. IBM SPSS Statistics version 23. IBM United Kingdom Limited, PO Box 41,
350 North Harbour , Portsmouth, Hampshire, PO6 3AU.
- 351 b. Augmentin® 500mg/100mg powder for solution for injection.
352 GlaxoSmithKline UK, Stockley Park West, Uxbridge Middlesex UB11 1BT.
353 United Kingdom.
- 354 c. Zinacef® 1.5g powder for solution for injection. GlaxoSmithKline
355 UK, Stockley Park West, Uxbridge Middlesex UB11 1BT. United Kingdom.
- 356 d. Dimazon® 50 mg/ml solution for injection. NOAH, MSD Animal Health.
357 Walton Manor, Walton, Milton Keynes MK7 7AJ, United Kingdom
- 358 e. Dexafort® 4 mg/ml suspension for injection. NOAH, MSD Animal
359 Health. Walton Manor, Walton, Milton Keynes MK7 7AJ, United Kingdom

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425 Figure 1: Dorsoventral and right lateral thoracic radiographs of a 4 month-old
 426 dog with negative-pressure pulmonary edema.

427 There is a diffuse alveolar pattern with indistinct margins more marked in the
 428 left caudal, left cranial and right caudal lung lobes on the dorsoventral view and
 429 in the dorsocaudal region in the lateral view.

430

431 Table 1: Summary of blood tests results obtained on admission from dogs with
 432 NPPE. TP: total protein.

433

Parameter	Number of cases where test was performed	SI units Mean \pm SD Median (range)	Reference interval	Conventional units Mean \pm SD Median (range)	Reference interval
PCV	25	0.39 \pm 0.06	0.37-0.55	39.7 \pm 5.8 %	37-55

TP	23	60 (44-85) g/L	60-75	6 (4.4-8.5) g/dL	6-7.5
pH	18	7.381 (7.083-7.453)	7.35-7.46	7.381 (7.083-7.453)	7.35-7.46
PCO ₂	18	4.9 (3.7-12) KPa	4.3-5.7	37 (27.6-89.5) mmHg	32-43
HCO ₃ ⁻	11	21.8 ± 1.9 mmol/L	18-26	21.8 ± 1.9 mEq/L	18-26
BE	10	-3.0 ± 1.8 mmol/L	-5-1	-3.0 ± 1.8 mEq/L	-5-1
Lactate	14	1.6 ± 1.0 mmol/L	0.5-2	14.4 ± 9 mg/dL	4.5-18
Na	19	144.5 ± 4.8 mmol/L	140-150	144.5 ± 4.8 mEq/L	140-150
K	19	4.1 ± 0.7 mmol/L	3.9-4.9	4.1 ± 0.7 mEq/L	3.9-4.9
Cl	12	112.7 ± 4.5 mmol/L	109-120	112.7 ± 4.5 mEq/L	109-120
Ionised calcium	15	1.32 ± 0.15 mmol/L	1.25-1.5	5.28 ± 0.6 mg/dL	5-6

Total calcium	11	2.6 ± 0.3 mmol/L	2.1 – 2.6	10.4 ± 1.2 mg/dL	8.4 – 10.4
Blood glucose	19	6.7 (5.6-11) mmol/L	3.6-6.2	120.7 (100.9-198.2) mg/dL	64.9-111.7
Urea	14	6.7 ± 2.3 mmol/L	1.8-10.7	18.8 ± 6.4 mg/dL	5-30
Creatinine	17	58.9 ± 18.5 umol/L	61.9-159.1	0.67 ± 0.21 mg/dL	0.7 – 1.8
Albumin	11	30.9 ± 2.3 g/L	25-37	3.1 ± 0.2 g/dL	2.5-3.7
Total bilirubin	11	0.35 (0-4.0) umol/L	0-15.9	0.02 (0-0.23) mg/dL	0-0.93
ALT	11	27 (18-1192) U/L	16-91	27 (18-1192) U/L	16-91
ALP	11	134 ± 44 U/L	20-155	134 ± 44 U/L	20-155
WBC	14	17.6 ± 5.4 10 ⁹ /L	5.3-19.8	17.6 ± 5.4 10 ³ /uL	5.3-19.8

Platelet count	14	360 ± 127 10 ⁹ /L	177-398	360 ± 127 10 ³ /uL	177-398
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435 Table 2: Comparison between survivors and non-survivors of patients'
 436 characteristics, type of injury and physical examination findings in dogs with
 437 NPPE.

438

Parameter		Survivors	Non-survivors	p value
Sex	Male	16	5	0.676
	Female	12	2	
Sexually intact		26	6	0.499
Age (months)		4 (2-90)	4 (2.5-60)	0.732
Weight (kg)		6.4(1.7-37.2)	9(2.7-19.2)	0.466
Type of injury	Category 1	9	1	0.376
	Category 2	6	0	
	Category 3	10	4	
	Category 4	2	1	
	Category 5	1	1	
Mentation	Alert	15	0	0.022
	Obtunded	5	5	

	Anesthetized	1	0	
Heart rate		140(80-180)	160(56-180)	0.247
Respiratory rate		80(32-180)	90(20-200)	0.960
Mucous membranes color	Pale	3	2	0.010
	Pink	20	0	
	Cyanotic	2	2	
	White	2	0	
Temperature (°C)		38.2(35.9- 38.8)	37.7 (34.9- 39.7)	0.358

439

440

441 Table 3: Comparison between survivors and non-survivors of diagnostic test
 442 results and treatments in dogs with NPPE. The number of times each test was
 443 performed can be found on table 1. SpO₂: blood oxygen saturation measured
 444 with pulse oximetry, TP: total protein.
 445

Parameter	Survivors	Non-survivors	p value
PCO ₂	4.9 (3.7-6.7) KPa 37.2(27.6- 50.4) mmHg	7.7 (4.6- 11.9) KPa 58(34.4- 89.5) mmHg	0.203
pH	7.379 (7.240-- 7.490)	7.261 (7.083- 7.440)	0.641
SpO ₂	91(81-99) %	87(56-91) %	0.365
Lactate	2.2 ± 1.5 mmol/L 19.8 ± 13.5 mg/dL	1.4 ± 0.1 mmol/L 12.6 ± 0.9 mg/dL	0.480
Na	145±5 mmol/L 145±5 mEq/L	143±1 mmol/L 143±1 mEq/L	0.660

K	4.1±0.5 mmol/L 4.1±0.5 mEq/L	3.5±0.1 mmol/L 3.5±0.1 mEq/L	0.153
Cl	111±5 mmol/L 111±5 mEq/L	110±6 mmol/L 110±6 mEq/L	0.775
Blood glucose	6.7 (5.6-11) mmol/L 120.7(100.9- 198.2) (mg/dL)	7.1 (6.6-7.6) mmol/L 127.9(118.9- 136.9) (mg/dL)	1
Creatinine	70.7 ± 17.7 mmol/L 0.8 ± 0.2 mg/dL	44.2 ± 35.4 mmol/L 0.5 ± 0.4 (mg/dL)	0.311
PCV	0.4 ± 0.05 40 ± 5 %	0.39 ± 0.09 39 ± 9 %	0.832
TP	60 (44-72) g/L 6 (4.4-7.2) (g/dL)	56 (52-85) g/L 5.6 (5.2-8.5) (g/dL)	0.667

WBC		16.8 ± 5.6 10 ³ /uL	15.9 ± 2.8 10 ³ /uL	0.828
Platelet count		381 ± 121 (10 ³ /uL)	230 ± 87 (10 ³ /uL)	0.119
All lung lobes affected		9	4	0.174
Pattern of infiltrate	Alveolar	22	4	0.406
	Interstitial	1	0	
	Interstitial to alveolar	3	1	
Oxygen administered		26	7	1.000
Treatment with furosemide		15	3	0.466
Treatment with glucocorticoids		6	3	0.242
Mechanical ventilation		2	5	<0.001