RESEARCH PAPER

Development of a severity scoring system for acute haemorrhage in anaesthetized domestic cats: the CABSS score

Gareth E Zeiler[a,b,c], Andrea Fuller[c], Eva Rioja[d], Peter Kamerman[c], Roxanne K Buck[a], Friederike Pohlin[a] & Brighton T Dzikiti[a,e]

[a]Department of Companion Animal Clinical Studies, Faculty of Veterinary Science, University of Pretoria, Pretoria, South Africa

[b]Anaesthesia and Critical Care Services, Valley Farm Animal Hospital, Pretoria, South Africa

[c]Brain Function Research Group, School of Physiology, University of the Witwatersrand, Johannesburg, South Africa

[d]Optivet Referrals, Havant, Hampshire, United Kingdom

[e]Clinical Sciences Department, Ross University School of Veterinary Medicine, Basseterre, Saint Kitts and Nevis

Correspondence: Gareth E Zeiler, Department of Companion Animal Clinical Studies, Faculty of Veterinary Science, University of Pretoria, Private Bag X04, Onderstepoort, 0110, South Africa. E-mail: gareth.zeiler@up.ac.za

Abstract

Objective To determine whether physiological, haematological, biochemical or electrolyte variables can predict severe haemorrhage in cats.

Study design Randomized crossover study whereby each cat underwent mild and severe haemorrhage, with a 2 month period between events.

Animals A group of six domestic cats aged 21 ± 1 months and weighing 4.9 ± 1.2 kg, mean ± standard deviation.

Methods Cats were anaesthetized (buprenorphine, alfaxalone, isoflurane in oxygen at a fixed end-tidal concentration of 1.7%) before the haemorrhage event. In total, 34 variables were measured twice (prehaemorrhage and posthaemorrhage). The difference and percent change for each variable were compared between haemorrhage events (paired t test). Significant variables were placed into 13 different ratios (posthaemorrhage value of one variable divided by a posthaemorrhage value of a second variable) and compared (paired t test), and Cohen's d (d) was calculated. Receiver operating characteristic curves were plotted and cut-off values for weak, moderate and strong indicators of severe haemorrhage were obtained.

Results The blood loss was 4.5 ± 1.1 mL kg^{-1} and 26.8 ± 5.5 mL kg^{-1} for mild and severe haemorrhage events, respectively. The most significant variables with large effect sizes were heart rate (HR), systolic arterial blood pressure (SAP), end-tidal carbon dioxide ($P_{E'}CO_2$), serum albumin, haematocrit and actual bicarbonate ion concentration [HCO_3^-(act)]. The most robust ratios were: 1) shock index ($d = -2.8$; HR:SAP); 2) HR:$P_{E'}CO_2$ ($d = -2.9$); 3) serum albumin: haematocrit ($d = 1.5$); and 4) HR:HCO_3^-(act) ($d = -1.6$). These ratios were included in the final proposed Cat Acute Bleeding Scoring System (CABSS).

Conclusions and clinical relevance Cats subjected to mild and severe haemorrhage demonstrated statistically and clinically relevant changes whereby four ratios could be created to make up the CABSS. The ratios detected and quantified the presence of severe haemorrhage in anaesthetized cats.

Keywords cat, haemorrhage, intraoperative haemorrhage, scoring system.

Introduction

Life-threatening haemorrhage occurs when more than 40% of the total circulating blood volume is lost acutely (Mylankal & Wyatt 2013). In veterinary species, once 30% or more blood volume has been lost acutely, compensatory mechanisms may fail and signs of haemorrhagic shock develop (Jutkowitz 2004). The mortality rate in domestic cats as a consequence of such haemorrhage is unknown; in humans, unexpected and uncontrolled intraoperative haemorrhage increased the mortality rate from less than 1% to over 20% (Copeland et al 1991).

Advances in surgical technique and anaesthetic management allow for more complex procedures to be successfully undertaken, but nonetheless the risk of significant haemorrhage is still present (Bellenger et al 1996; DeLay

2016; Hanson et al 2017). Most healthy animals can tolerate an acute loss of 10% of their circulating blood volume without warranting volume resuscitation. There are several methods used to estimate the volume of intraoperative blood loss, which include measuring the quantity of blood in suction canisters, counting blood-soaked swabs (sponges) and estimating blood volume loss on surgical drapes (Jutkowitz 2004). Indirect methods used to assess haemorrhage include measurement of the haemoglobin [(Hb) or haematocrit (Ht)], albumin or total serum solids (Jutkowitz 2004). However, these indirect methods are only useful to assess blood loss after compensatory fluid shifts have taken place, which occurs at least 2 hours following an acute haemorrhage event (Jutkowitz 2004). Consequently, volume resuscitation in cats experiencing severe haemorrhage may be delayed. Furthermore, the relatively small blood volume of healthy cats, which ranges from 52.6 ± 6.8 to 59.6 ± 5.8 mL kg^{-1}, makes the determination of blood loss a challenge (Groom et al 1965; Mott 1968). Additionally, determining blood loss is especially challenging when there is insidious bleeding within the thoracic and peritoneal cavities that is masked by overlying organs or when the field of vision is limited (thoracoscopy and laparoscopy). Intraoperative haemorrhage is likely under-recognized in cats and a possible risk factor for many of the reported cardiovascular-related perianaesthetic deaths (Brodbelt 2010).

Currently, there are no scoring systems used to aid in the detection or quantification of acute haemorrhage in conscious or anaesthetized companion animals (Reineke 2018), but they are commonplace in human medicine (Pons et al 1985; Baskett 1990; Yucel et al 2006; Chico-Fernandez et al 2011; Ogura et al 2014; Callcut et al 2016). The scoring systems applied in human medicine are used to identify patients in haemorrhagic shock, to guide resuscitation or as an early transfusion trigger, often before patients present to a hospital (Terceros-Almanza et al 2019). We speculate that the ideal scoring system should be one that 1) is easy to calculate, 2) makes use of physiological variables that reflect an early response to haemorrhage, 3) includes variables that are reflected by changes in blood composition, and 4) is composed only of variables that are obtainable at a single time point once acute haemorrhage is suspected.

The aim of the present study was to determine if there are any immediately quantifiable physiological, haematological, biochemical or electrolyte variables that can be used in the Cat Acute Bleeding Scoring System (CABSS) to predict an acute severe haemorrhage event in domestic cats. We hypothesized that none of the variable values obtained before a mild or a severe haemorrhage event would be different from those measured after the event in anaesthetized cats.

Material and methods

Study design, animals and housing

A group of six domestic cats (mean ± standard deviation, age 21 ± 1 months, mass 4.9 ± 1.2 kg) were used based on availability in this balanced, randomized, crossover study where the interventions were mild and severe acute haemorrhage during anaesthesia,. A 2 month period between haemorrhagic events was used. The order of treatments was randomized using an online randomizer using a balanced single block design (www.randomization.com; Dallal 2008). The cats were sourced from various locations as kittens and were then housed together in the University of Pretoria Biomedical Research Centre's indoor-outdoor purpose-built cattery until their body weight was >3 kg. The study was approved by the Ethics Committees of the University of Pretoria (v006-15) and University of Witwatersrand (2017-10-68-C-AREC). This study was part of a larger fluid resuscitation project and only data relevant to this present study are reported.

A clinical examination that included venous blood sampling from the jugular vein for blood analysis (haematology, albumin, blood urea nitrogen, creatinine, electrolytes) was performed 1 week prior to the haemorrhage event to determine the health status of the cat.

Haemorrhage event procedures

Prehaemorrhage period

On the morning of data collection, each cat was transferred to the theatre complex of the hospital and placed in a standard ward cage. The cat was weighed and underwent a clinical examination. Each animal was premedicated with buprenorphine hydrochloride (0.02 mg kg^{-1}; Temgesic 0.3 mg mL^{-1}; Beckitt Benckiser Healthcare, RSA) administered intramuscularly. The cat was transferred to the induction room 45 minutes later and an indwelling catheter (22 gauge; Jelco; Smiths Medical International, UK) was inserted aseptically into one of the cephalic veins and secured in place. General anaesthesia was induced with alfaxalone (Alfaxalone; Afrivet, RSA) administered intravenously to effect. A cuffed polyvinylchloride endotracheal tube (4.0–4.5 mm internal diameter; Teleflex Incorporated, RSA) was placed into the trachea after a single spray of lidocaine (10 mg per spray; Xylocaine; AstraZeneca Pharmaceuticals, RSA) onto the *rima glottidis*. The endotracheal tube was then connected to a circle breathing system (15 mm internal diameter, Compact paediatric breathing system; Intersurgical, RSA). General anaesthesia was maintained with isoflurane (Isofor; Safeline Pharmaceuticals, RSA) in oxygen at a fixed fresh gas flow rate of 80 mL kg^{-1} $minute^{-1}$. The

vaporizer was initially set to 2%, target end-tidal isoflurane ($F_{E'}$Iso) concentration was standardized for the study and maintained at 1.7% throughout the procedures (Shaughnessy & Hofmeister 2014). The cat was placed in dorsal recumbency and its ventral neck region (rostral intermandibular region to the second intercostal space of the thorax) was shaved and surgically scrubbed. The cat was transferred to the theatre, placed in dorsal recumbency and instrumented.

A catheter (22 gauge, 50 mm, Arrow arterial catheterization set; Arrow International, PA, USA) was inserted into the right (superficialized 15 months earlier during gonadectomy) carotid artery using a cut-down technique to facilitate measurement of direct arterial blood pressure (electronic transducer zeroed to atmospheric air pressure at the level of the right atrium; BD DTX; Becton & Dickson Medical, NY, USA), and arterial blood samples were taken intermittently for blood gas analyses. A catheter (22 gauge, 50 mm, Arrow arterial catheterization set; Arrow International) was inserted percutaneously into the left jugular vein for intermittent blood sampling. The Seldinger technique was used to insert the catheters into the carotid artery and jugular vein (Seldinger 1953). A three-lead electrocardiogram (ECG) was assessed by attaching ECG pads and electrodes placed on the digital pads (RA, LA, RL; lead II) to determine the heart rate (HR) and rhythm. A paediatric pitot spirometer with an in-built gas sampling line was attached between the endotracheal tube and breathing system to measure expiratory tidal volumes (V_{Texp}), respiratory rate (f_R) and respiratory gas tensions including end-tidal carbon dioxide ($P_{E'}CO_2$) and $F_{E'}$Iso. A transmittance pulse oximetry probe was placed on to the tongue to measure peripheral oxygen haemoglobin saturation (SpO_2). A thermistor probe (reusable general purpose adult probe; GE Healthcare, Finland) was inserted into the oesophagus to a depth of the fourth intercostal space.

All probe leads were connected to a multiparameter monitor (Cardiocap 5; Datex, Finland). A balanced electrolyte crystalloid fluid (lactated Ringer's solution; Fresenius Kabi, RSA) was infused at a constant rate of 5 mL kg^{-1} $hour^{-1}$ throughout the procedures via the cephalic catheter.

Haemorrhage period

Prehaemorrhage data were collected before the cat underwent the assigned haemorrhage event (24 ± 6 minutes after induction of anaesthesia). After the haemorrhage event was complete, posthaemorrhage data were collected immediately. Pre- and posthaemorrhage event data collection included physiological, haematological, biochemical, electrolyte and blood gas variables. The order of data collection was standardized and began with all blood sampling followed by the recording of physiological variables.

The physiological variables measured included HR, arterial blood pressures [systolic (SAP), mean (MAP) and diastolic (DAP)], SpO_2, f_R, V_{Texp}, $P_{E'}CO_2$, $F_{E'}$Iso and body temperature (T). The haematological variables were differentiated cell counts, Hb concentration and Ht measured from venous blood samples (ethylenediaminetetraacetic acid collection tube; BD, Becton Dickinson and Company, UK). The biochemical variables were serum albumin, blood urea nitrogen, creatinine, glucose and lactate measured from venous blood sample (serum clot activator tube; BD, Becton Dickinson and Company). The electrolytes measured were sodium, potassium, ionized calcium, total magnesium, chloride and phosphorus ion concentrations also measured from venous blood samples (blood gas and serum clot activator tube). Partial pressure of arterial oxygen (PaO_2) and arterial and venous carbon dioxide ($PaCO_2$ and $PvCO_2$) and acid-base balance [pH, bicarbonate ion (HCO_3^-), base excess] were measured in arterial and venous blood samples (heparinized syringes; BD A-line; Becton Dickinson and Company). The total amount of blood drawn per data collection was 10 mL (3 mL waste and 7 mL samples).

The mild haemorrhage event was defined as blood loss sustained during blood sampling which amounted to 20 mL in total, regardless of the cat's body mass. The posthaemorrhage blood sample was obtained 15 minutes after the prehaemorrhage blood sample.

The severe haemorrhage event was defined as blood loss sustained during purposeful collection of blood into a semi-closed system using citrate-phosphate-dextrose (4 mL; JMS blood bag, 450 mL; JMS Singapore PTE LTD, Singapore) primed 20 mL syringes via the jugular catheter. We assumed that the cat's total blood volume was 55 mL kg^{-1} and a severe haemorrhage event was an acute blood loss of more than 22 mL kg^{-1} (> 40% assumed circulating volume). Manual blood withdrawal continued at a targeted rate of 2 mL kg^{-1} $minute^{-1}$ (15 minutes) until one of two endpoints. The endpoint was either a maximum withdrawal of 30 mL kg^{-1} of blood, which did not include the blood sampling volume, or a MAP of < 48 mmHg that persisted for at least 3 minutes. The total amount of blood drawn was calculated as a sum of the blood sampling (20 mL) and the purposefully bled volume.

The haemorrhage time was measured using a stopwatch and started after prehaemorrhage data collection and ended when the haemorrhage endpoint was reached. On completion of the haemorrhage event, the cat entered a fluid resuscitation phase of the project that is not reported here. All cats survived and were rehomed through an adoption processes 1 month after completing the project.

Data analysis

Data were assessed for similar distribution types by plotting histograms and comparing descriptive statistics for each

variable within the mild and severe haemorrhage data sets. Outlier's of high and low values were tested by using the Grubb's test. Data were considered normally distributed and no outliers were detected. All calculations using blood gas values were performed using data expressed in mmHg rather than kPa. The absolute and percent change from pre-haemorrhage values were calculated for all variables. The haemorrhage time, difference and percent change values for each variable were compared between the mild and severe haemorrhage events using a paired t test. The 95% confidence interval for the mean difference and the p value for each comparison were assessed to screen variables initially and thereby to identify those that could be incorporated into the scoring system. This initial screening was supplemented by effect size calculations for each variable (difference and percent change) using Cohen's d (d). An effect size of $d > 0.8$ was considered large and clinically meaningful (Sullivan & Feinn 2012). All variables that met the initial screening criteria were then placed into various unitless ratios (post-haemorrhage value of one variable divided by a post-haemorrhage value of a second variable) to identify ratios that could potentially be incorporated into the scoring system. The variables included in the ratios were based on published ratios (shock index: Allgower & Burri 1967) or clinical insight and mathematical ease of use. These ratios were calculated for mild and severe haemorrhage events and compared with each other using the paired t test. Receiver operating characteristic (ROC) curves were plotted and the area under the curve calculated for the most robust ratios. Cut-off values for weak, moderate and strong indicators of severe haemorrhage were obtained by examining the ROC curve, whereby mild haemorrhage events had to have a 100% specificity (indicating the cat had not undergone severe haemorrhage) and severe haemorrhage events had to have 100% sensitivity (indicating the cat had undergone severe haemorrhage). The sensitivity and specificity values were calculated for weak, moderate and strong indicators of severe haemorrhage. Weak values were defined as 100% specific and the highest value for sensitivity at the interval; and strong values had to be 100% sensitive and the highest value for specificity at the interval. Moderate values were in between the weak and strong values. The positive and negative likelihood ratios and predictive values for each cut-off value of the indicators were then estimated. The predictive values were calculated using a prevalence of 50% for severe haemorrhage.

Data were analysed using commercially available software (MiniTab Version 18.1; Minitab Inc., PA, USA; and MedCalc Version 19.0.3; MedCalc Software, Belgium) and significance interpreted at $p < 0.05$. Data are reported as mean (± standard deviation).

Results

All cats completed both haemorrhage events. The $F_{E'}$Iso was 1.7 ± 0.2% and 1.8 ± 0.1% during the mild and severe haemorrhage events, respectively (t value: 1.37; $p = 0.229$). Blood loss was 4.5 ± 1.1 mL kg^{-1} for the mild haemorrhage event and 26.8 ± 5.5 mL kg^{-1} for the severe haemorrhage event. Haemorrhage time was 15.3 ± 0.4 minutes for the mild haemorrhage event and was not different from 17.2 ± 2.6 minutes for the severe haemorrhage event (t value: 1.53; $p = 0.186$). The MAP after the mild haemorrhage event was 64 ± 4 mmHg and significantly greater than 44 ± 4 mmHg following the severe haemorrhage event (t value: 10.49; $p < 0.01$). These outcomes indicate that all cats were subjected to haemorrhage events that met the study requirements.

The outcomes of the initial screening analyses of the 34 variables are presented in Table 1. The qualifying screening physiological variables were HR ($d = -2.9$), arterial blood pressures [SAP ($d = 3.7$), MAP ($d = 3.4$) and DAP ($d = 2.5$)] and $P_{E'}CO_2$ ($d = 1.7$). Of the haematological variables, Hb concentration ($d = -1.8$) and leukocyte count ($d = 1.3$) qualified as potential screening variables. The Ht ($d = -1.4$) was also included in the ratio analysis to determine its suitability because the trend in difference and percent change were broadly similar in magnitude and direction of change of Hb. Of the biochemical variables, serum albumin ($d = 2.3$) demonstrated a more robust difference and percent change than creatinine ($d = -2.1$) and glucose ($d = -1.3$), both of which fitted the screening criteria. Potassium ($d = -1.5$) was the only electrolyte that demonstrated a difference and percent change between haemorrhagic events. With respect to blood gases variables, $PaCO_2$ ($d = 2.2$) and PaO_2 ($d = -2.6$) and actual bicarbonate ion concentration [HCO_3^-(act)] ($d = 2.7$) qualified as screening variables. The $PaCO_2$ tended to change in the same direction as $P_{E'}CO_2$.

The 15 variables that met the initial screening criteria qualifications were placed into 13 different ratios for further analysis (Table 2). Several ratios are not reported owing to either a lack of differentiation between haemorrhagic states or because the values were mathematically difficult to interpret. The most robust ratios demonstrating clinically relevant sensitivity and specificity within each indicator cut-off range were: the 1) shock index ($d = -2.8$; HR:SAP); 2) HR:$P_{E'}CO_2$ ($d = -2.9$); 3) serum albumin:Ht ($d = 1.5$); and 4) HR:HCO_3^-(act) ($d = -1.6$). The cut-off values for weak, moderate and strong indicators of severe haemorrhage are presented in Table 3 and Fig. 1. These values, which were derived from the ROC curves, yielded clinically meaningful sensitivities and specificities, as corroborated by meaningful likelihood ratios and predictive values. These four ratios were included in the final proposed CABSS (Table 4).

Table 1 Difference and percent change in physiological, haematological, biochemical, electrolyte, blood gas and acid-base variables pre- and posthaemorrhage in anaesthetized cats undergoing mild (<10 mL kg^{-1}) and severe haemorrhage (>22 mL kg^{-1}) events. The variables were ordered from largest to smallest size effect (Cohen *d* value) and only values > 0.8 were considered as large and clinically meaningful.

Variable	Value type	Mild haemorrhage		Severe haemorrhage		Paired *t* test		
		Mean	SD	Mean	SD	95% CI - μ_d	Cohen *d*	(*t* value; *p* value)
Physiological								
SAP (mmHg)	Difference	−1	4	−23	9	(14; 31)	3.7	(7.1; 0.001)
	% Change	−0.6	4.6	−26.5	9.4	(16.6; 35.3)	3.8	(7.13; 0.001)
MAP (mmHg)	Difference	−5	8	−27	6	(18; 27)	3.4	(13.44; <0.001)
	% Change	−5.9	11.4	−38.0	5.2	(24; 40)	4.0	(10.38; 0.002)
Heart rate (beats minute−1)	Difference	3	8	49	23	(−66; −26)	−2.9	(−5.97; 0.002)
	% Change	1.9	6.7	44.5	21.0	(−62.8; −22.4)	−3.0	(−5.42; 0.003)
DAP (mmHg)	Difference	−5	8	−21	6	(11; 20)	2.5	(8.69; <0.001)
	% Change	−7.9	12.4	−35.9	6.5	(19.3; 36.6)	3.1	(8.29; <0.001)
$P_E'CO_2$ (mmHg)	Difference	0	2	−5	4	(2; 9)	1.2	(3.57; 0.016)
	% Change	0.2	5.5	−11.0	9.9	(5.2; 17.3)	1.5	(4.77; 0.005)
VTexp (mL)	Difference	1	1	0	3	(−3; 4)	0.4	(0.47; 0.655)
	% Change	3.9	4.9	2.5	13.2	(−16.5; 19.4)	0.2	(0.21; 0.843)
fR (breaths $minute^{-1}$)	Difference	0	5	1	6	(−4; 2)	−0.2	(−1.05; 0.341)
	% Change	−3.8	14.8	18.2	29.0	(−42.7; −1.4)	−1.0	(−2.74; 0.041)
Temperature (°C)	Difference	−0.1	0.2	−0.1	0.4	(−0.42; 0.32)	−0.2	(−0.35; 0.741)
	% Change	−0.4	0.4	−0.2	1.2	(−1.2; 0.9)	−0.2	(−0.34; 0.746)
SpO_2 (%)	Difference	0	1	1	1	(−1.4; 1.1)	−0.2	(−0.35; 0.741)
	% Change	0.0	1,1	0.2	0.4	(−1.4; 1.1)	−0.2	(−0.34; 0.751)
Haematology								
Haemoglobin (mg dL^{-1})	Difference	−3	2	10	10	(−24; −1)	−1.8	(−2.73; 0.041)
	% Change	−3.2	2.5	11.2	12.5	(−28.2; −0.5)	−1.7	(−2.67; 0.044)
Erythrocyte count	Difference	5.9	0.7	6.8	1.0	(−1.6; −0.3)	−1.5	(−3.51; 0.094)
	% Change	−1.7	2.3	9.9	12.9	(−26.9; 3.6)	−1.4	(−1.96; 0.107)
Haematocrit (L/L)	Difference	0.00	0.01	0.03	0.03	(−0.07; 0.01)	−1.4	(−2.19; 0.080)
	% Change	−1.8	3.1	10.4	13.1	(−26.8; 2.5)	−1.4	(−2.13; 0.086)
Leukocyte count	Difference	−0.4	0.5	−1.6	1.3	(0.1; 2.3)	1.3	(2.78; 0.039)
	% Change	−3.8	3.4	−18.8	11.6	(2.6; 27.5)	1.9	(3.11; 0.027)
Thrombocyte count	Difference	4.8	44	−38	59	(−32; 116)	0.9	(1.46; 0.204)
	% Change	1.8	15.5	−11.1	18.7	(−11.1; 36.9)	0.8	(1.38; 0.225)
Neutrophil count	Difference	−0.04	0.28	−0.41	1.01	(−0.83; 1.58)	0.6	(0.80; 0.460)
	% Change	0.0	5.6	−9.5	15.2	(−9.0; 27.8)	0.9	(1.31; 0.246)
Lymphocyte count	Difference	−0.3	0.5	−0.4	1.3	(−0.9; 1.1)	0.1	(0.32; 0.758)
	% Change	−7.5	13.2	1.8	41.2	(−52.5; 33.8)	−0.3	(−0.56; 0.601)
Biochemistry								
Albumin (g L^{-1})	Difference	−1	0	−4	2	(1; 5)	2.3	(4.4; 0.007)
	% Change	−2.5	2.0	−12.1	6.2	(4.3; 15.0)	2.3	(4.66; 0.006)
Creatinine (mmol L^{-1})	Difference	−1	3	13	10	(−25; −3)	−2.1	(−3.32; 0.021)
	% Change	−0.8	2.1	12.6	9.2	(−23.1; −3.7)	−2.2	(−3.55; 0.016)
Glucose (mmol L^{-1})	Difference	0.0	0.2	0.8	1.0	(−1.9; 0.17)	−1.3	(−2.16; 0.083)
	% Change	−1.2	3.8	14.9	16.5	(−32.7; 0.5)	−1.5	(−2.49; 0.055)
BUN (mmol L^{-1})	Difference	0	0	1	0	(−0.9; 0.1)	−1.3	(−1.87; 0.120)
	% Change	1.1	1.8	5.8	5.1	(−10.9; 1.6)	−1.3	(−1.90; 0.115)
Lactate (mmol L^{-1})	Difference	0.0	0.3	0.0	0.5	(−0.6; 0.6)	<0.1	(−0.07; 0.945)
	% Change	3.9	20.6	3.2	30.4	(−40.8; 42.3)	<0.1	(0.04; 0.966)
Electrolytes								
Potassium (mmol L^{-1})	Difference	0.1	0.1	0.3	0.2	(−0.4; −0.1)	−1.5	(−3.53; 0.017)
	% Change	2.8	2.5	9.6	6.4	(−11.9; −1.7)	−1.5	(−3.41; 0.019)
Magnesium (mmol $^{L-1}$)	Difference	0.8	0.1	0.8	0.1	(−0.03; 0.09)	1.0	(1.31; 0.067)
	% Change	0.3	3.5	−2.2	2.0	(−0.3; 5.2)	0.9	(2.33; 0.067)
Phosphorus (mmol L^{-1})	Difference	0	0	0	0	(−0.3; 0.1)	−0.8	(−1.05; 0.341)
	% Change	2.5	2.9	6.1	6.9	(−13.0; 5.8)	−0.8	(−0.99; 0.367)

(*continued on next page*)

Table 1 (*continued*)

Variable	Value type	Mild haemorrhage		Severe haemorrhage		Paired *t* test		
		Mean	SD	Mean	SD	95% CI - μ_d	Cohen *d*	(*t* value; *p* value)
Chloride (mmol L^{-1})	Difference	−1	4	1	2	(−5; 2)	−0.6	(−1.36; 0.233)
	% Change	−0.9	3.3	0.6	2.0	(−4.5; 1.5)	−0.6	(−1.28; 0.257)
Sodium (mmol L^{-1})	Difference	−2	6	0	6	(−8; 5)	−0.3	(−0.65; 0.542)
	% Change	−1.3	3.9	−0.3	4.4	(−5.7; 3.6)	−0.3	(−0.58; 0.585)
Ionised calcium (mmol L^{-1})	Difference	0	0.1	0	0.1	(−0.1; 0.1)	−0.1	(−0.17; 0.869)
	% Change	0.7	6.2	1.0	8.8	(−11.2; 10.5)	−0.1	(−0.09; 0.934)
Blood gases and acid-base balance								
HCO_3^-(act) (mmol L^{-1})	Difference	0.1	0.4	−1.5	0.8	(0.9; 2.2)	2.7	(6.01; 0.002)
	% Change	0.3	2.0	−7.8	4.2	(4.8; 11.4)	2.7	(6.30; 0.001)
PaO_2 (mmHg)	Difference	−14	23	53	32	(−91; −43)	−2.6	(−7.00; 0.001)
	% Change	−4.0	6.3	14.4	9.2	(−25.2; −11.6)	−2.6	(−6.93; 0.001)
$PaCO_2$ (mmHg)	Difference	0	1	−5	3	(3; 8)	2.2	(5.01; 0.004)
	% Change	0.4	4.4	−12.3	8.6	(6.9; 18.5)	2.0	(5.61; 0.002)
Base excess (mmol L^{-1})	Difference	0.1	0.4	−1.1	1.1	(0.1; 2.2)	1.6	(2.84; 0.036)
	% Change	−1.2	6.7	22.9	36.7	(−1.2; 22.9)	−1.0	(−1.68; 0.154)
$PvCO_2$ (mmHg)	Difference	−2	4	−4	2	(−2; 6)	0.8	(1.44; 0.210)
	% Change	−3	7	−7	5	(−3.4; 12.1)	0.9	(1.61; 0.169)
pH	Difference	0.00	0.02	0.02	0.04	(−0.05; 0.01)	−0.8	(−1.58; 0.175)
	% Change	0.0	0.2	0.3	0.5	(−0.7; 0.2)	−0.8	(−1.60; 0.171)
Bicarb (std) (mmol L^{-1})	Difference	−1.7	3.8	−0.7	0.9	(−5.4; 3.4)	−0.4	(−0.59; 0.578)
	% Change	−8.6	19.7	−3.2	4.1	(−27.7; 17.1)	−0.4	(−0.61; 0.567)

HCO_3^-(act), actual bicarbonate ion concentration; Bicarb (std), standard bicarbonate ion concentration; BUN, blood urea nitrogen; DAP, diastolic arterial blood pressure; fR, respiratory rate; MAP, mean arterial blood pressure; PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; Pe′CO2, end-tidal carbon dioxide; PvCO2, venous partial pressure of carbon dioxide; SAP, systolic arterial blood pressure; SD, standard deviation; SpO2, peripheral oxygen haemoglobin saturation; VTexp, expiratory tidal volume; 95% CI - μd, 95% confidence interval of the difference between the means.

Table 2 Comparison of screening qualifying ratios using the paired *t* test and Cohen's *d* in anaesthetized cats undergoing mild (< 10 mL kg^{-1}) and severe haemorrhage (> 22 mL kg^{-1}) events.

Ratio	Mild haemorrhage		Severe haemorrhage		Paired *t* test		
	Mean	SD	Mean	SD	95% CI - μ_d	Cohen *d*	(*t* value; *p*)
HR:$P_{E'}CO_2$	2.5	0.5	4.2	0.7	(−2.3; −1.2)	−2.9	(−8.53; 0.001)
HR:SAP (SI)	1.3	0.3	2.5	0.6	(−1.7; −0.8)	−2.8	(−7.44; 0.001)
HR:$PaCO_2$	2.6	0.6	4.2	1.1	(−2.9; −0.3)	−2.0	(−3.45; 0.026)
HCO_3^-(act):Ht	71	7	57	10	(5; 22)	1.8	(3.91; 0.010)
HR:HCO_3^-(act)	6	2	10	3	(−5; −2)	−1.6	(−5.97; 0.006)
Alb:Ht	108	15	85	18	(11; 35)	1.5	(4.82; 0.005)
Alb:Hb	0.34	0.05	0.26	0.06	(0.03; 0.11)	1.5	(4.30; 0.008)

Alb:Hb, serum albumin concentration to haemoglobin concentration; Alb:Ht, serum albumin concentration to haematocrit; HCO_3^-(act):Ht: actual bicarbonate ion concentration to haematocrit; HR:HCO_3^-(act): heart rate to actual bicarbonate ion concentration; HR:$PaCO_2$, heart rate to arterial partial pressure of carbon dioxide; HR:$P_{E'}CO_2$, heart rate to end-tidal carbon dioxide; SD, standard deviation; SI, shock index calculated by dividing the heart rate by the systolic arterial blood pressure; 95% CI - μ_d, 95% confidence interval of the difference between the means.

The serum albumin:Ht values could be substituted for the serum albumin:Hb values (d = 1.5); however, the ratio values obtained were mathematically difficult to interpret. This was because the ratios were very small (i.e. had a large number of decimal places) and cannot be recommended (Table 2). The HR:$P_{E'}CO_2$ ratios could be substituted by the HR:$PaCO_2$ (d = −2.0) and conform to the suggested indicator cut-off ranges for that ratio. However, the HR:$PvCO_2$ cannot be recommended as a substitute for the HR:$P_{E'}CO_2$ ratio because it did not pass the initial screening criteria.

Discussion

Anaesthetized cats that had undergone mild or severe haemorrhage demonstrated reliable differences in various pre- and posthaemorrhage variables assessed in the present study. The

Table 3 Sensitivity, specificity and positive and negative likelihood ratios and predicative values of four ratios that make up an acute haemorrhage scoring system in anaesthetized cats. The cut-off values divide the ratio value into weak, moderate and strong indicator strengths whereby a cat obtaining values within the strong indicator had sustained a severe haemorrhage in excess of 22 mL kg^{-1}.

Ratio	Indicator	Value	Sensitivity	Specificity	+LR	−LR	+PV	−PV	AUC	Z-statistic
HR:SAP (SI)	Weak	<1.3	83	100	6	0.17	100	86	0.986	24.7
	Moderate	1.4 to 1.9	100	83	6	0.01	86	100		
	Strong	>2.0	100	67	3	0.01	75	100		
Alb:Ht	Weak	>120	17	100	2	0.83	100	55	0.833	2.6
	Moderate	91 to 119	67	83	4	0.40	80	71		
	Strong	<90	100	67	3	0.01	75	100		
HR:$P_{E'}CO_2$	Weak	<2.5	60	100	6	0.40	100	75	>0.999	–
	Moderate	2.6 to 3.6	100	83	6	0.01	83	100		
	Strong	>3.7	100	67	3	0.01	71	100		
HR:HCO_3^-(act)	Weak	< 6.5	83	100	5	0.17	100	86	0.917	4.6
	Moderate	6.6 to 9.8	83	83	5	0.20	83	83		
	Strong	> 9.9	100	50	2	0.01	67	100		

Alb:Ht, serum albumin concentration to haematocrit; AUC, area under the curve; HR:HCO_3^-(act), heart rate to actual bicarbonate ion concentration; HR:$P_{E'}CO_2$, heart rate to end-tidal carbon dioxide; +LR, positive likelihood ratio; −LR, negative likelihood ratio; +PV, positive predictive value; −PV, negative predictive value; SI, shock index calculated by dividing the heart rate by the systolic arterial blood pressure.

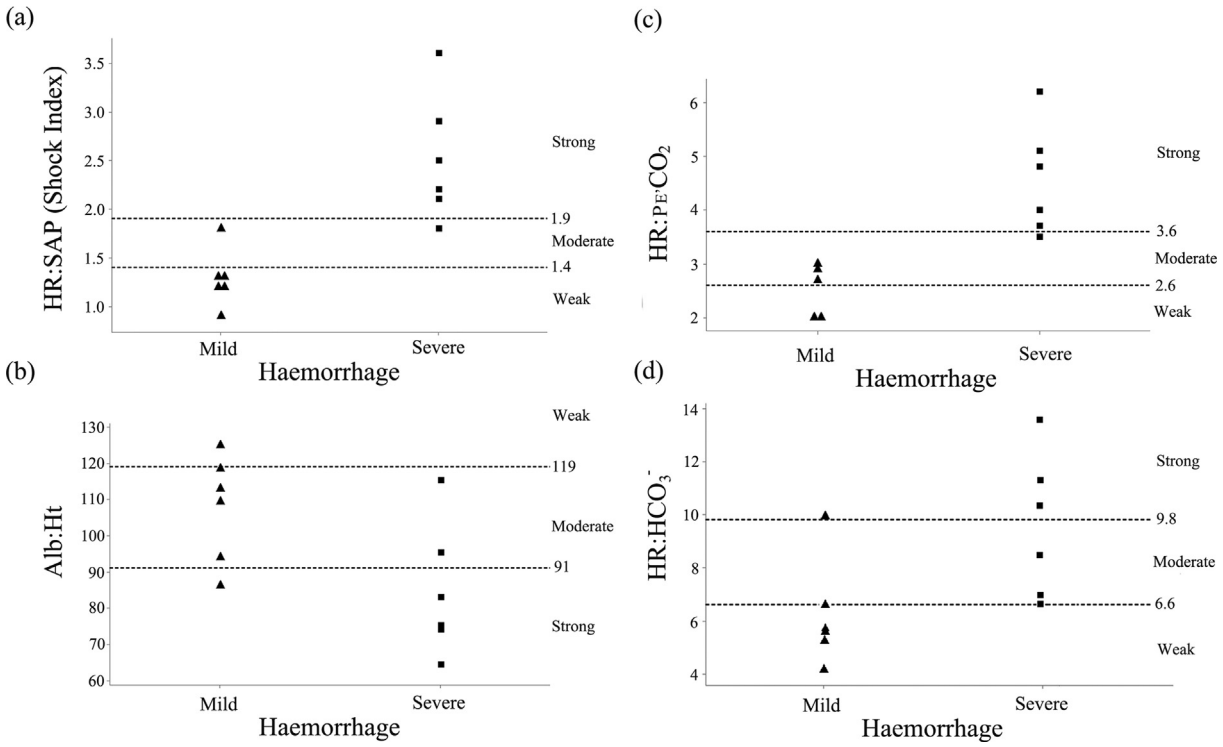

Figure 1 Individual value plots of a) shock index, b) serum albumin:haematocrit, c) heart rate:end-tidal carbon dioxide, and d) heart rate:actual bicarbonate ion concentration ratios in cats that underwent a mild and severe haemorrhage event while under general anaesthesia. The horizontal reference lines indicate the cut-off values for the indicators (weak, moderate, strong) of severe haemorrhage. Values within the strong area of the plot indicate that a severe haemorrhage probably occurred. Alb:Ht, serum albumin concentration to haematocrit; HR:HCO_3^-(act), heart rate to actual bicarbonate ion concentration; HR:$P_{E'}CO_2$, heart rate to end-tidal carbon dioxide; HR:SAP, shock index is calculated by dividing heart rate by systolic arterial blood pressure. A single measurement for the variables used in the respective ratio was obtained soon after the haemorrhage.

Table 4 Cat Acute Bleeding Scoring System (CABSS), an intraoperative haemorrhage scoring system for the detection and quantification of severe haemorrhage in anaesthetized adult cats. User instructions: all ratios should be calculated to accurately detect and quantify blood loss during acute intraoperative haemorrhage. In the event that not all variables can be measured then, at a minimum, the HR:SAP and HR:$P_{E'}CO_2$ should be calculated.

Ratio	Direction of change over time[a]	Indicator strength		
		Weak	Moderate	Strong
Must calculate these two ratios as minimum				
HR:SAP (SI)	Increasing	<1.3	1.4–1.9	>2.0
HR:$PE'CO_2$	Increasing	<2.5	2.6–3.6	>3.7
Assess one or both ratios below to increase suspicion of severe haemorrhage				
Alb:Ht	Decreasing	>120	91–119	<90
HR:HCO_3^-(act)	Increasing	<6.5	6.6–9.8	<9.9
Interpretation of ratios				
Haemorrhage		Mild		Severe
Blood loss (mL kg^{-1})		<10	11–21	>22

Alb, serum albumin concentration (g L^{-1}); HR, heart rate; Ht, haematocrit (L/L^{-1}); $P_{E'}CO_2$, end-tidal carbon dioxide (mmHg); SAP, systolic arterial blood pressure (mmHg); SI, shock index.

[a]Change in direction of the variable is compared to preoperative values.

most notably different variables were HR, SAP, $P_{E'}CO_2$, serum albumin, Ht and HCO_3^-(act). Four easy-to-calculate ratios were derived from these variables including: 1) shock index; 2) serum albumin:Ht; 3) HR: $P_{E'}CO_2$; and 4) HR:HCO_3^-(act). These ratios make up the proposed CABSS, which aims to quantify haemorrhage by indicating (weak, moderate and strong) the likelihood of severe haemorrhage in this species.

The shock index, which was first described in 1967, is perhaps the most commonly investigated human scoring system that has been studied in dogs (Allgower & Burri 1967). A shock index of >1.0 is considered a sensitive (85%) and specific (80%) tool for the detection of small volume blood loss (≈18% blood loss) in healthy canine blood donors. It is more useful when compared to monitoring the Ht, lactate and total plasma proteins (McGowan et al 2017). Furthermore, the shock index was also a useful triage tool in dogs presenting with haemorrhagic shock. Values > 0.9 indicate that further investigation is required to identify severe and ongoing haemorrhage and thereby to stabilize the animal (Peterson et al 2013). The shock index uses the classic cardiovascular variables that change over time in response to hypovolaemia where the HR increases to compensate for the decrease in blood pressure. However, human anaesthesiologists Schultz & McConachie (2015) caution the use of vital signs alone during haemorrhage. This is because certain patients develop uncommon neurovascular reflexes, which means they do not demonstrate the classical physiological response to hypovolaemia and instead present with seemingly normal vital signs.

Furthermore, cats that were administered medetomidine as part of a general anaesthetic protocol have a shock index of < 1.0 (Zeiler et al 2014). However, the cardiovascular effects of medetomidine or other drugs used during the perianaesthetic period might mask the classic cardiovascular response to hypovolaemia, which may confound intraoperative scoring during severe haemorrhage. Also, cats may present with a normal HR or develop bradycardia during shock and therefore the shock index could be <1.0 (Murphy & Hibbert 2013). To avoid misdiagnosis, we have incorporated other ratios into our proposed scoring system.

The HR:$P_{E'}CO_2$ ratio demonstrated an increasing trend whereby the HR increased and the $P_{E'}CO_2$ decreased as the volume of blood loss increased. The decreasing $P_{E'}CO_2$ and $PaCO_2$ and the increase in HR suggest a decrease in cardiac output (Dubin et al 1990; Long et al 2017). Furthermore, Dubin et al (1990) found that the $PvCO_2$ increases during low cardiac output states such as hypovolaemia, thus widening the gap between $PaCO_2$ and $PvCO_2$. Our data agree with the findings reported by Dubin et al (1990). Venous hypercarbia and arterial hypocarbia are described in dogs and rabbits during low flow states as a result of haemorrhagic shock (Benjamin et al 1987; Williams et al 2014). This increase in venous hypercarbia during low flow states confirms our finding that $PvCO_2$ cannot be used as a substitute for $P_{E'}CO_2$.

The serum albumin:Ht ratio reflected acute changes within the intravascular compartment during haemorrhage. The Ht increased and serum albumin concentration decreased; therefore, the serum albumin:Ht ratio demonstrated a consistent decrease. The rise in Ht in the cats subjected to severe haemorrhage has been inconsistently described in other experimental models, rather a decrease has been described (Groom et al 1965; Mott 1968). This inconsistency could be related to the rate of haemorrhage and the subsequent time at which Ht measurements were made. In our study, cats were bled over 15 minutes and sampled immediately after the haemorrhagic event, whereas other authors took blood samples over several hours. It is proposed that this longer time period allowed fluid shifts to take place between the interstitial and intravascular spaces, which was reflected in a decrease in

Ht values (Jutkowitz 2004). However, in dogs, an increase in Ht occurred after acute haemorrhage and before fluid shifts had taken place or before fluid resuscitation (Kirby 1995; McGowan et al 2017). In the serum albumin:Ht ratio, the serum albumin concentration decreased possibly because of the loss of whole blood (Kirby 1995).

The HR:HCO_3^-(act) concentration ratio also reflected acute changes within the intravascular compartment during haemorrhage. The HCO_3^-(act) concentration is rarely reported in cats, especially for those in haemorrhagic shock. Regardless, it is a value that is calculated by modern blood gas analysers and reflects the concentration of HCO_3^- within the blood (Lawrrie & Golda 1979). The HR:HCO_3^-(act) concentration ratio accurately reflected the extent of blood loss and, therefore, it was incorporated in the CABSS. The authors believe that this ratio warrants further investigation in future studies. The CABSS may be a useful tool in the diagnosis and quantification of haemorrhage in cats undergoing surgical procedures under general anaesthesia. To make use of the CABSS, we recommend that all ratios should be calculated to accurately detect and quantify blood loss during acute intraoperative haemorrhage. In the event that not all variables can be measured, then at a minimum, the HR:SAP and HR:$P_{E'}CO_2$ should be calculated. Furthermore, the CABSS could be a useful tool to gauge haemorrhage volumes in cats that have experienced a traumatic event and present to veterinary hospitals within 30 minutes of sustaining injury.

The present study has two notable limitations. The sample size is small so only had the power to reliably detect large effects, and even then, the magnitude of the effect sizes is potentially biased. Nevertheless, the variables included in the ratios are physiologically justified, and they yielded robust thresholds for differentiating mild and severe haemorrhage. Furthermore, the observations herein should assist future researchers in estimating adequate sample sizes to validate this scoring system under various clinical conditions. The second limitation is that the study was conducted in anaesthetized cats under controlled conditions. Therefore, extrapolation of our findings to conscious animals, those experiencing trauma or those given different drugs during anaesthesia will require further investigation. However, the authors speculate that the variables that make up the CABSS ratios should result in a similar outcome regardless of the clinical presentation. Our assumption is based on the use of an anaesthetic protocol that had minimal effects on the cardiovascular system. Furthermore, we did not titrate the isoflurane concentration (1 × minimum alveolar concentration) recommended for surgery in cats (Shaughnessy & Hofmeister 2014) to effect.

Conclusion

Cats subjected to mild and severe haemorrhage demonstrated statistically and clinically relevant change in HR, SAP, $P_{E'}CO_2$, serum albumin, Ht and HCO_3^-(act) concentration. These variables were used in four ratios as follows: 1) HR:SAP or shock index; 2) serum Alb:Ht; 3) HR:$P_{E'}CO_2$; and 4) HR:HCO_3^-(act) concentration. The ratios that were created are unitless and when assessed together, aided in the detection and quantification of severe haemorrhage in this study. The four ratios make up the proposed CABSS which could be a tool for detecting and quantifying acute haemorrhage in cats.

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Authors' contributions

GEZ, RKB, FP: completed the data collection. All authors participated in study design and contributed with data analysis and manuscript editing.

Conflict of interest

Authors declare no conflict of interest.

References

Allgower M, Burri C (1967) Shockindex. Dt Med Wschr 43, 1947–1950.

Baskett PJ (1990) ABC of major trauma. Management of hypovolaemic shock. Br Med J 300, 1453–1457.

Bellenger CR, Hunt GB, Goldsmid SE, Pearson MRB (1996) Outcomes of thoracic surgery in dogs and cats. Aus Vet J 1, 25–30.

Benjamin E, Paluch TA, Berger SR et al. (1987) Venous hypercarbia in canine hemorrhagic shock. Crit Care Med 15, 516–518.

Brodbelt D (2010) Feline anesthetic deaths in veterinary practice. Top Companion Anim Med 25, 189–194.

Callcut RA, Cripps MW, Nelson MF et al. (2016) The massive transfusion score as a decision aid for resuscitation: learning when to turn the massive transfusion protocol on and off. J Trauma Acute Care Surg 80, 450–456.

Copeland GP, Jones D, Walters M (1991) POSSUM: a scoring system for surgical audit. Br J Surg 78, 355–360.

Chico-Fernandez M, Garcia-Fuentes C, Alonso-Fernandez MA et al. (2011) Massive transfusion predictive score in trauma. Experience of a transfusion registry. Med Intensiva 35, 546–551.

Dallal GE (2008) Randomizing the order in which subjects receive multiple treatments. Last accessed 31 March 2017. http://www.randomization.com.

DeLay J (2016) Perianesthetic mortality in domestic animals: a retrospective study of postmortem lesions and review of autopsy procedures. Vet Path 53, 1078–1086.

Dubin A, Silva C, Calvo G et al. (1990) End-tidal CO2 pressure in the monitoring of cardiac output during canine hemorrhagic shock. J Crit Care 5, 42—46.

Groom AC, Rowlands S, Thomas HW (1965) Some circulatory responses to haemorrhage in the cat: a critical level of blood volume for the onset of hypotension. J Physiol 172, 385—405.

Hanson KR, Pigott AM, Linklater AKJ (2017) Incidence of blood transfusion requirement and factors associated with transfusion following liver lobectomy in dogs and cats: 72 cases (2007-2015). J Am Vet Med Assoc 251, 929—934.

Jutkowitz LA (2004) Blood transfusions in the perioperative period. Clin Techniq Sm Anim Prac 19, 75—82.

Lawrrie A, Golda BP (1979) Actual or standard bicarbonate. Lancet 28, 201—202.

Long B, Koyfman A, Vivirito MA (2017) Capnography in the emergency department: A review of uses, waveforms and limitations. J Emerg Med 53, 829—842.

Kirby R (1995) Transfusion therapy in emergency and critical care medicine. Vet Clin N Am: Sm Anim Prac 25, 1365—1386.

McGowan EE, Marryott K, Drobatz KJ et al. (2017) Evaluation of the use of shock index in identifying acute blood loss in healthy blood donor dogs. J Vet Emerg Critic Care 27, 524—531.

Mott JC (1968) The effect of haemorrhage on haemoglobin concentration, blood volume and arterial pressure in kittens and cats. J Physiol 194, 659—667.

Murphy K, Hibbert A (2013) The flat cat part 1. J Fel Med Surg 15, 175—188.

Mylankal KJ, Wyatt MG (2013) Control of major haemorrhage and damage control surgery. Surg 31, 574—581.

Ogura T, Nakamura Y, Nakano M et al. (2014) Predicting the need for massive transfusion in trauma patients: the traumatic bleeding severity score. J Trauma Acute Care Surg 76, 1243—1250.

Peterson KL, Hardy BT, Hall K (2013) Assessment of shock index in healthy dogs and dogs in hemorrhagic shock. J Vet Emerg Crit Care 23, 545—550.

Pons PT, Honigman B, Moore EE et al. (1985) Prehospital advanced trauma life support for critical penetrating wounds to the thorax and abdomen. J Trauma 25, 828—832.

Reineke EL (2018) Trauma overview. In: Textbook of Small Animal Emergency Medicine (2nd edition). Drobatz KJ, Hopper K, Rozanski EA, Silverstein DC (eds). Wiley Blackwell, USA. pp. 1041—1051.

Schultz W, McConachie I (2015) Vital signs after haemorrhage — caution is appropriate. Trend Anaesth Crit Care 5, 89—92.

Seldinger SI (1953) Catheter replacement of the needle in percutaneous arteriography: a new technique. Acta Radiol 39, 368—376.

Shaughnessy MR, Hofmeister EH (2014) A systematic review of sevoflurane and isoflurane minimum alveolar concentration in domestic cats. Vet Anaesth Analg 41, 1—13.

Sullivan GM, Feinn R (2012) Using effect size — or why the P value is not enough. J Grad Med Educ 4, 279—282.

Terceros-Almanza LJ, Garcia-Fuentes C, Bermejo-Aznarez S et al. (2019) Prediction of massive bleeding in a prehospital setting: validation of six scoring systems. Med Intensiva 43, 131—138.

Williams KB, Christmas AB, Heniford BT et al. (2014) Arterial vs venous blood gas differences during hemorrhagic shock. World J Crit Care Med 4, 55—60.

Yucel N, Lefering R, Maegele M et al. (2006) Trauma associated severe haemorrhage (TASH)-score: probability of mass transfusion as surrogate for life threatening haemorrhage after multiple trauma. J Trauma 60, 1228—1237.

Zeiler GE, Dzikiti BT, Fosgate GT et al. (2014) Anaesthetic, analgesic and cardiorespiratory effects of intramuscular medetomidine-ketamine combination alone or with morphine or tramadol for orchiectomy in cats. Vet Anaesth Analg 41, 411—420.

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