End-tidal to arterial carbon dioxide gradient in traumatic brain injury after prehospital emergency anesthesia is associated with in-hospital mortality: a retrospective observational study

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Research

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Abstract

Background Early definitive airway protection and normoventilation are key principles in the treatment of severe traumatic brain injury. These are currently guided by end tidal CO_2 as a proxy for $PaCO_2$. We assessed whether the difference between end tidal CO_2 and $PaCO_2$ at hospital admission is associated with in-hospital mortality.

Method We conducted a retrospective observational cohort study of consecutive patients with traumatic brain injury who were intubated and transported by Helicopter Emergency Medical Services to a Level 1 trauma center between January 2014 and December 2019. We assessed the association between the CO_2 gap—defined as the difference between end tidal CO_2 and $PaCO_2$—and in-hospital mortality using multivariate logistic regression models.

Results 105 patients were included in this study. The mean ±SD CO_2 gap at admission was 1.64 (± 1.09) kPa and significantly greater in non-survivors than survivors (2.26 ±1.30 kPa vs. 1.42 ±0.92 kPa, p<.001). The correlation between $EtCO_2$ and $PaCO_2$ at admission was low (Pearson's r=.287). The mean CO_2 gap after 24 hours was only 0.64 ±0.82 kPa, and no longer significantly different between non-survivors and survivors. The multivariate logistic regression model showed that the CO_2 gap was independently associated with increased mortality in this cohort and associated with a 2.7-fold increased mortality for every 1 kPa increase in the CO_2 gap (OR 2.692, 95% CI 1.293 to 5.646, p=.009).

Conclusions This study demonstrates that the difference between $EtCO_2$ and $PaCO_2$ is significantly associated with in-hospital mortality in patients with traumatic brain injury. $EtCO_2$ was significantly lower than $PaCO_2$, making it an unreliable proxy for $PaCO_2$ when aiming for normocapnic ventilation. The higher-than-expected CO2 gap will lead to iatrogenic hypoventilation when normocapnic ventilation is aimed at, and might thereby increase in-hospital mortality.

Background

Treatment recommendations in traumatic brain injury (TBI) include early definitive airway protection as well as normoventilation with a target arterial partial pressure of CO_2 ($PaCO_2$) of 4.6-5.9 kPa (35 to 45 mmHg) [1,2]. The effects of hypo- or hyperventilation on cerebral blood flow (CBF), with the potential for hypoxemia or hyperemia of cerebral tissue and their negative impact on outcome, have been widely studied [3–7]. Using $PaCO_2$ to monitor ventilation requires arterial blood gas (ABG) analyses, but the necessary lab equipment is not yet widely available in the prehospital environment. Therefore end-tidal CO_2 ($EtCO_2$) determined by capnography has been used as a surrogate marker to estimate $PaCO_2$ assuming a reliable correlation between $EtCO_2$ and $PaCO_2$ [8].

Capnography is considered the gold standard, both to determine correct placement of a definitive airway and to guide ventilation during emergency care [9,10]. The assumed correlation between $EtCO_2$ and

$PaCO_2$ has been known to be accompanied by a tension difference of CO_2 ranging anywhere between 0.26 and 0.66kPa (2 and 5 mmHg) in otherwise healthy individuals undergoing anesthesia [11–16]. However, major trauma accompanying TBI can negatively influence ventilation and perfusion, making the interpolation of $PaCO_2$ from $EtCO_2$ in trauma patients unreliable [17–19]. As expected, subgroup analyses have shown the best correlation between $EtCO_2$ and $PaCO_2$ in isolated TBI when compared to other trauma patients [20].

The primary aim of this study is to describe the correlation between $EtCO_2$ and $PaCO_2$ at the time of admission in patients hospitalized with TBI. Furthermore, we investigated the predictive value of tension difference of CO_2 between $EtCO_2$ and $PaCO_2$ (CO_2 gap) for in-hospital mortality.

Methods

Study participants, setting and ethics approval

This retrospective observational single-center cohort study included all consecutive patients with TBI who were intubated on the scene and transported by the helicopter emergency medical service (HEMS) (Swiss Air-Rescue, Rega) to a Level 1 trauma center (Kantonsspital St. Gallen, Switzerland) between January 1st of 2014 and December 31st of 2019. Exclusion criteria were patients who were not intubated before admission, patients with traumatic injuries requiring intubation for other reasons than TBI, and secondary transport missions including patients with traumatic brain injury who were transported from another hospital to this trauma center.

The local ethics committee of St. Gallen (EKOS) granted permission to use patient data without individual consent according to the federal act on research involving human beings and the ordinance on human research with the exception of clinical trials. The permission also covered the use of patient data regarding the HEMS operation (EKOS St. Gallen 7.7.2020, BASEC Nr. 2020-01737 EKOS 20/122).

Data and definitions

Baseline characteristics of patients were obtained from electronic hospital records. Laboratory findings were obtained by automated retrieval using the unique patient identification number in the hospital records. $EtCO_2$ was measured using main-stream capnographs. Information on the ventilator settings at admission was prospectively entered into the patients' electronic hospital records.

Outcome information (i.e., survival status) was documented prospectively as part of the routine electronic hospital records and obtained from the corresponding record.

The Injury Severity Score Thorax was determined at admission. $EtCO_2$, systolic blood pressure, pulse and SpO_2 were analyzed on admission to the Emergency Room (ER) as well as 24 hours after admission.

Statistics

Patients' characteristics were summarized and presented in tables. Continuous variables were summarized by mean ± SD (standard deviation) if normally distributed or by median and IQR (interquartile range) if skewed. Normality was tested using the Shapiro-Wilk test. Categorical variables were summarized with counts and percentages for each level of the variable. Outliers were assessed using the Grubbs test for continuous variables if normally distributed.

Correlation between $EtCO_2$ and $PaCO_2$ was assessed using Pearson's correlation coefficient and visualized using a scatter plot. Disagreement between $EtCO_2$ and $PaCO_2$ was visualized using a Bland-Altman plot [21]. Differences in the CO_2 gap between survivors and non-survivors were tested using the Mann-Whitney-Wilcoxon Test. The association between the CO_2 gap and the in-hospital mortality was further assessed using a multivariable logistic regression model. To minimize confounding, variables potentially associated with the respiratory system and in-hospital mortality were defined a priori based on a literature review and clinical experience [22]. The variables included age, heart rate, systolic blood pressure, peripheral capillary oxygen saturation, pressure of oxygen in arterial blood (paO2), and severity of chest injury documented by the ISS (Injury Severity Score) thoracic sub-score. All variables were coded as continuous variables. Complete case analyses were performed due to the low number of missing data and therefore the low risk of bias. As a sensitivity analysis, the association of the time difference between the initial arterial blood gas sample and the first recorded $EtCO_2$ was explored using a univariate linear regression model.

Two-sided p-values of <0.05 were considered as statistically significant. All statistical analyses were performed using R Studio 3.6.0 on macOS 10.15.7.

Results

This study adheres to the STROBE Statement (Strengthening the Reporting of Observational Studies in Epidemiology) [23]. From January 2014 to December 2019 a total of 181 patients were admitted to our trauma center by HEMS after TBI and intubation. Seventy-six patients were excluded. Reasons were mechanisms of injury besides TBI, an alternate reason for unconsciousness, missing ISS, $EtCO_2$ or $PaCO_2$ data, or early extubation in the ER.

Of the 105 patients admitted to the ICU, 28 (27%) died and 77 (73%) were discharged alive. Information on neurological function at discharge was not available.

The patients' baseline characteristics are displayed in Table 1. Of note, non-survivors were on average more than 20 years older than survivors and had a lower PaO_2 in the initial blood gas samples, p<0.001.

The correlation between $EtCO_2$ and $PaCO_2$ at admission was low, Pearson's r=.287, Figure 1. There was a significant difference between $EtCO_2$ and $PaCO_2$ at admission. The overall mean CO_2 gap at admission was 1.64 ±1.09 kPa and significantly larger in non-survivors than survivors, 2.26 ±1.30 kPa vs. 1.42 ±0.92 kPa, p<.001, see Table 2 and Figure 2. Of note, the CO_2 gap (visualized as mean bias on the Bland-Altman

plots) was more pronounced in patients with lower $EtCO_2$ values. This demonstrates that patients with $EtCO_2$ measures within the target range (4.6 to 5.9 kPa) were unwittingly hypercapnic [1,2]. The overall CO_2 gap decreased to 0.64 ±0.82 kPa at 24h after admission and was no longer significantly different between non-survivors and survivors, 0.78 ±0.70 kPa vs. 0.58 ±0.86, p=.108, see Table 2 and Figure 2.

The multivariate logistic regression model showed that the CO_2 gap was independently associated with increased mortality in intubated and mechanically ventilated patients with TBI. For every increase of the CO_2 gap by 1 kPa, mortality was 2.7 times higher, OR 2.692, 95%-CI 1.293 to 5.646, p=.009. Higher age was independently associated with an increased mortality rate as well, OR 1.842 for every increase of 10 years, 95% CI 1.106 to 2.641, p=.001. Systolic blood pressure, heart rate, thoracic trauma, SpO_2 and PaO_2 were not associated with survival status in this multivariate model, see Table 3 and Figure 4. Inclusion of further parameters from the arterial blood gas samples (ABG samples), the total ISS, or other cardiopulmonary parameters in the regression model led to multicollinearity; these parameters were therefore excluded from the final model.

The majority of $EtCO_2$ and $PaCO_2$ pairs were obtained within 30 minutes, n=60, 57%. As a sensitivity analysis the impact of the time interval between arterial blood gas sampling and the documentation of $EtCO_2$ from monitors on the CO_2 gap was assessed in a univariate linear regression model. This association was not significant, p=.165.

Discussion

Our results show that end-tidal capnography is an unreliable tool for monitoring and targeting invasive ventilation at least in the initial treatment of patients with severe TBI. Although the majority of the patients in this study were ventilated within the target range of $EtCO_2$ values, many were unwittingly hypercapnic in the first blood gas sample after arriving in the hospital. Our data show a large variability in the calculated CO_2 gap in this patient cohort and it was more pronounced in patients with lower $EtCO_2$. This underestimation of $PaCO_2$ when $EtCO_2$ was used to guide ventilation caused hypoventilation despite normal $EtCO_2$ values. An increased CO_2 gap and the resulting hypercapnia were associated with increased in-hospital mortality. This underlines the clinical importance of these findings and the need for either a more reliable surrogate parameter for $PaCO_2$ estimation or early $PaCO_2$ sampling in the prehospital management of patients with TBI.

The CO_2 gap

Previous studies have observed that the CO_2 gap is multifactorial, with possible causes including ventilation-perfusion mismatch, increased dead space, or, shock with impaired perfusion and temperature [11,24]. However, most of these factors influencing the CO_2 gap are not measurable, detectable or predictable in the initial treatment period in the field or ER. The ability to predict or gauge the CO_2 gap based on the patient's condition is consequently limited. In this context the CO_2 gap might be both, an

indicator of severity of injury, and a predictor of impaired survival in patients with severe traumatic brain injury.

Two recent publications investigated the CO_2 gap in critically ill patients after prehospital emergency anesthesia [25,26]. Their findings are in line with our results and showed only moderate correlation between $EtCO_2$ and $PaCO_2$, confirming that $EtCO_2$ alone should be used with caution to guide ventilation in the critically ill.

In a cohort of cardiac arrest patients, Suominen et al. showed an association between an increased CO_2 gap and in-hospital mortality 24 hours after return of spontaneous circulation (ROSC). Our data is in line with these findings and reinforces the plausibility of this association by controlling for potential confounding due to shock or hypoperfusion in a multivariate logistic regression model.

$EtCO_2$ as a surrogate marker

$PaCO_2$ is considered to be the major determinant of cerebral blood flow (CBF) through its effects on cerebral vascular tone [27]. This reinforces the importance of precise ventilatory control in the initial management of TBI. It is known that even modest hypercapnia can result in substantial increases in ICP and can cause dangerous cerebral ischemia when intracranial compliance is poor [28]. Therefore, we hypothesize that the hypoventilation due to underestimation of the arterial CO_2 using $EtCO_2$ as a surrogate marker leads to impaired CBF and thereby increases mortality.

Recent TBI guidelines rely on the assumption that the CO_2 gap is approximately 0.5 kPa (3.8 mmHg). However, these assumptions are based on data of individuals undergoing general anesthesia without major comorbidities or trauma [11,29]. In this study, the mean first $EtCO_2$ was 4.6 ±0.78 kPa, whereas the mean $PaCO_2$ was 6.26 ±1.03 kPa and far in excess of the target of 4.5 to 5.0 kPa. Therefore, relying on $EtCO_2$ as a surrogate for $PaCO_2$ provides a false sense of security, and providers may not achieve optimal prehospital $PaCO_2$. At present, no reliable alternative to direct ABG sampling seems to exist in order to approximate $PaCO_2$ reliably.

However, to our best knowledge, there is no data supporting the routine use of point-of-care blood gas analyses in patients mechanically ventilated in the field. This lack of data could be due to the fact that up to now the importance of point-of-care testing in prehospital care has been underestimated, due to the high reliance on proxy markers like $EtCO_2$. Further studies on the optimal timing of sampling after intubation and the beginning of mechanical ventilation, as well as the optimal sampling interval, are needed. We postulate that a single ABG sample post-intubation could gauge the individual CO_2 gap and ensure more reliable $EtCO_2$-guided ventilation.

Factors influencing mortality

Our data showed a significant age difference between survivors and non-survivors. Age was independently and significantly associated with mortality. Besides the fact that age might be a surrogate for unrecognized confounders due to comorbidities that negatively influence mortality, clinical decision-making may also play a role. In daily routine, palliation might be considered at an earlier stage in elderly trauma victims with limited rehabilitation potential, whereas younger trauma patients may receive maximum therapeutic interventions [30].

In our cohort, systolic blood pressure and ISS thorax scores were not significantly associated with mortality in the multivariate analysis.

Limitations

This study had several limitations. First, it is a retrospective and single-center cohort study with a limited sample size. However, data was almost complete and multivariate adjustments were performed. Second, in order to increase the number of eligible patients in this study, we included patients who had an ABG sample up to 30 min after hospital arrival. However, a sensitivity analysis showed that the observed gradient between $EtCO_2$ and $PaCO_2$ was not significantly associated with the time between arterial blood gas sampling and the documented $EtCO_2$. Still, it is possible that a proportion of the gradient between $EtCO_2$ and $PaCO_2$ was due to changes in ventilation settings during this period.

Conclusions

The CO_2 gap is an inconsistent phenomenon in pre-hospital anesthetized TBI patients, making $EtCO_2$ an unreliable proxy for $PaCO_2$ when aiming for normocapnic ventilation. The higher-than-expected CO_2 gap can lead to unaware iatrogenic hypoventilation and consequently hypercapnia, which is associated with increased in-hospital mortality.

Declarations

Ethics approval and consent to participate

The local ethics committee of St. Gallen (EKOS) granted permission to use patient data without individual consent according to the federal act on research involving human beings and the ordinance on human research with the exception of clinical trials. The permission also covered the use of patient data regarding the HEMS operation (EKOS St. Gallen 7.7.2020, BASEC Nr. 2020-01737 EKOS 20/122).

Consent for publication

Consent for publication was waived as per the ethics approval.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

UP, LM and PD designed the study. PD and UP performed Data collection. LM performed statistical analysis. UP, LM and PD drafted and finalized the manuscript. SJS, MF, JK, AE and RA reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Tables

Table 1: Baseline characteristics of patients

Variable	Overall	Survivors	Non-survivors
	n=105	n=77	n=28
Age, *years*	49.5 ± 22.6	43.4 ± 21.0	66.3 ± 18.1
Age <18 years, *n (%)*	9 (9)	8 (10)	1 (4)
Male gender, *n (%)*	71 (68)	51 (66)	20 (71)
ISS Total, *median (IQR)*	25 (17 to 34)	25 (14 to 34)	31 (25 to 38)
ISS = 75, *n (%)*	1 (1)	0	1 (4)
ISS Thorax, *median (IQR)*	0 (0 to 2)	0 (0 to 2)	0 (0 to 2)
Missing (ISS Thorax), *n (%)*	12 (11)	9 (12)	3 (11)
Cardiopulmonary parameters			
Systolic BP, *mmHg*	127 ± 33	127 ± 29	125 ± 43
Diastolic BP, *mmHg*	78 ± 28	80 ± 30	72 ± 21
Pulse, *bpm*	93 ± 26	92 ± 24	93 ± 32
SpO_2, *median (IQR)*	100 (98 to 100)	100 (98 to 100)	99.5 (94.8 to 100)
Temperature, *°C*	35.9 ± 0.93	35.9 ± 0.93	35.9 ± 0.98
Missing, *n (%)*	16	11	5
Arterial blood gas			
pH, *median (IQR)*	7.31 (7.26 to 7.35)	7.31 (7.28 to 7.36)	7.31 (7.19 to 7.33)
BE, *mmol/l median (IQR)*	-3.6 (-6.4 to -1.9)	-3.6 (-5.8 to -1.7)	-4.9 (-8.4 to -2.3)
HCO_3^-, *mmol/l median (IQR)*	21.9 (19.9 to 23.6)	21.5 (20.5 to 23.6)	21.1 (19.6 to 23.4)
Lactate, *mmol/l median (IQR)*	2.0 (1.2 to 3.4)	1.9 (1.2 to 2.7)	2.8 (1.4 to 4.5)
$PaCO_2$, *kPa median (IQR)* *	6.0 (5.5 to 6.8)	5.9 (5.5 to 6.6)	6.4 (5.7 to 6.8)
PaO_2, *kPa median (IQR)*	28.2 (17.6 to 48.9)	34.3 (19.6 to 51.5)	23.1 (14.9 to 29.8)
Hemoglobin, *g/l*	122 ± 21	122 ± 20	119 ±24
Glucose, *mmol/l median (IQR)*	8.0 (6.3 to 10.1)	7.5 (6.0 to 8.9)	10.2 (8.1 to 13.2)

Footnote:

Data was complete if not otherwise specified. Continuous variables are reported as mean ± SD = (standard deviation) if normally distributed and not stated otherwise.

BP = blood pressure; IQR = Interquartile range; ISS = injury severity score; bpm = beats per minute; SpO_2 = peripheral capillary oxygen saturation.

* $PaCO_2$ = Same parameter as shown in detail on Table 2 (initial measure).

Table 2: $PaCO_2$ and $EtCO_2$ pairs at admission and after 24 hours

Variable	Overall	Survivors	Non-survivors	p value
	n=105	n=77	n=28	
Initial measures	105 (100)	76 (100)	28 (100)	
CO_2 gap, *kPa*	1.64 ± 1.09	1.42 ± 0.92	2.26 ± 1.30	<0.001
$PaCO_2$, *kPa*	6.26 ± 1.03	6.17 ± 0.96	6.48 ± 1.18	
$EtCO_2$, *kPa*	4.61 ± 0.78	4.76 ± 0.74	4.23 ± 0.76	
$PaCO_2$ within 15 min of $EtCO_2$	42 (40)	30 (39)	13 (46)	
$PaCO_2$ within 30 min of $EtCO_2$	60 (57)	39 (51)	21 (75)	
Measures within 24h	75 (71)	53 (70)	22 (79)	
CO_2 gap, *kPa*	0.64 ± 0.82	0.58 ± 0.86	0.78 ± 0.70	0.108
$PaCO_2$, *kPa*	5.12 ± 0.60	5.19 ± 0.59	4.91 ± 0.58	
$EtCO_2$, *kPa*	4.46 ± 0.79	4.59 ± 0.82	4.15 ± 0.63	
Hours since admission	18.6 ± 7.8	19 ± 8.0	17.7 ± 7.5	

Footnote:

Data was complete. Numbers are presented with percentages of total in parentheses. Continuous variables are reported as mean ± SD (standard deviation). The CO_2 gap and the $PaCO_2$ variables were skewed; however, the mean ± SD was presented due to the use of these parameters in the Bland-Altman plots. CO_2 gap = PaO_2 - $EtCO_2$

Table 3: Multivariate logistic regression model of survival

Variable	Odds Ratio	95% CI of OR	Standard error	p value
CO_2 gap, *kPa*	2.692	1.283 to 5.646	0.385	0.009
Age, *10 years*	1.063	1.026 to 1.102	0.018	0.001
Systolic BP, *mmHg*	1.002	0.986 to 1.018	0.008	0.822
Pulse, *bpm*	0.984	0.960 to 1.009	0.013	0.199
SpO_2, *%*	0.960	0.810 to 1.137	0.106	0.635
PaO_2, *kPa*	0.966	0.926 to 1.007	0.022	0.101
ISS Thorax	1.030	0.683 to 1.554	0.214	0.887

Footnote:

Complete case analysis available for 93 patients. Twelve patients were excluded from the analysis due to missing data (see Table 1). Units of measure and abbreviations as described in Tables 1 and 2.

Figures

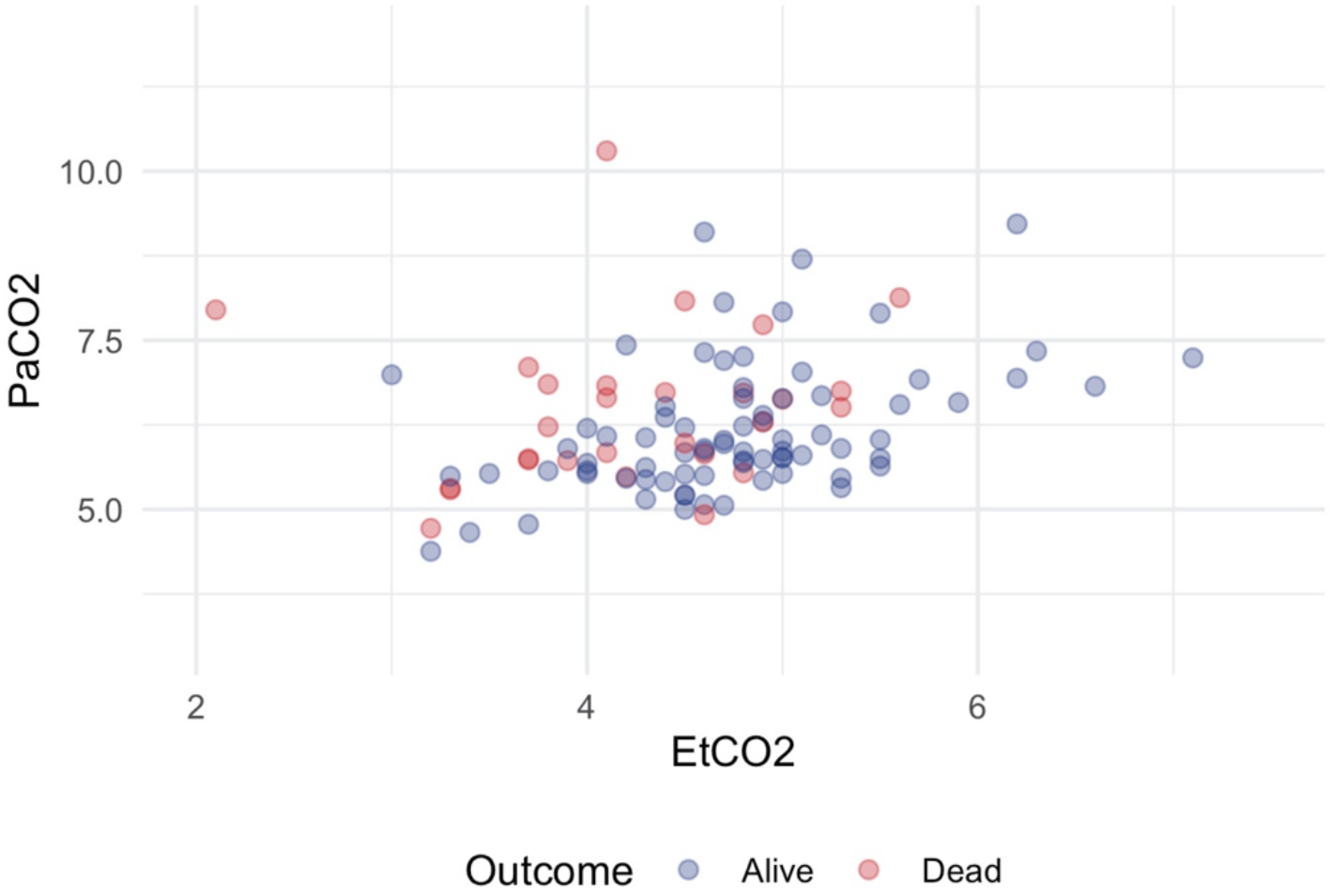

Figure 1

Correlation of PaCO2 and EtCO2. Footnote: Pearson's correlation coefficient overall r = 0.287, for survivors r = 0.438, for non-survivors r = 0.150. PaCO2 and EtCO2 in kPa

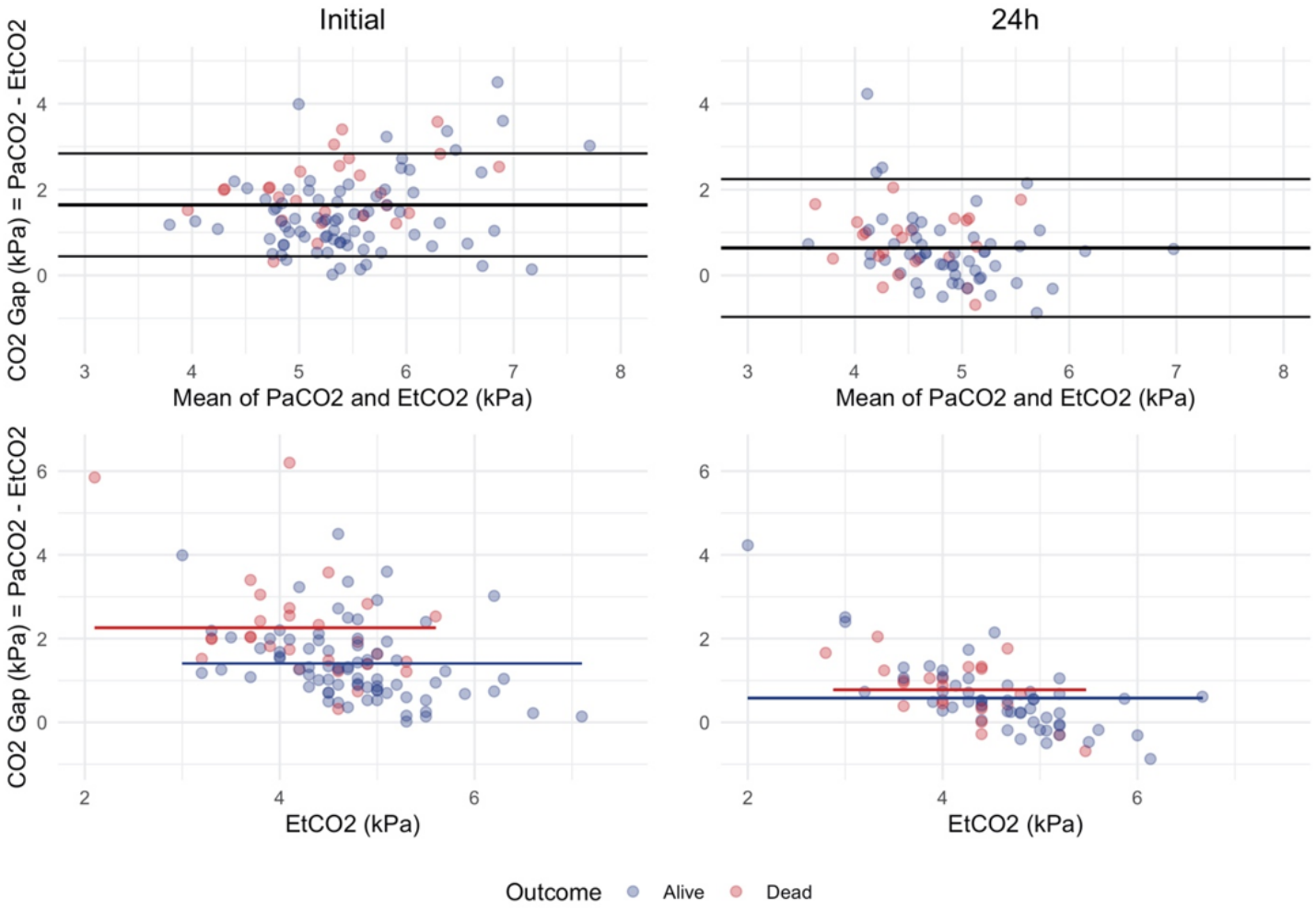

Figure 2

Bland-Altman plots and point plots comparing PaCO2 and EtCO2. Footnote: Top row: Bland-Altman plots for all available pairs of PaCO2 and EtCO2 at different time points. Bottom row: corresponding point plots for the same data. The red and blue lines illustrate the mean CO2 gap for deceased and surviving patients, respectively. The mean CO2 gap lines are trimmed, illustrating the EtCO2 range for both groups, respectively. Difference between PaCO2 and EtCO2 was highly significant for the initial pairs ($p<0.001$) but not for the pairs after 24 hours (see Table 2).

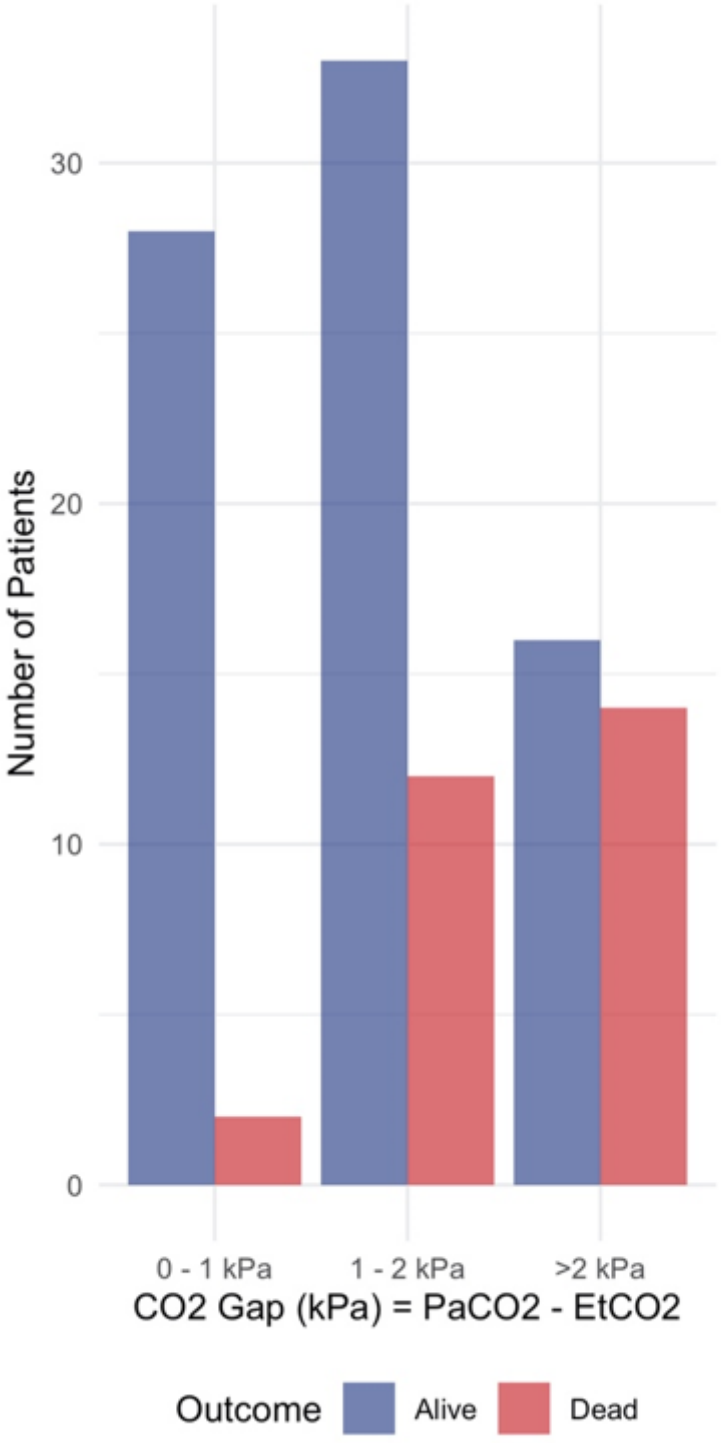

Figure 3

Bar diagram showing survival for CO2 gap groups. Footnote: Bar diagram showing outcome by groups of CO2 gap measured initially.

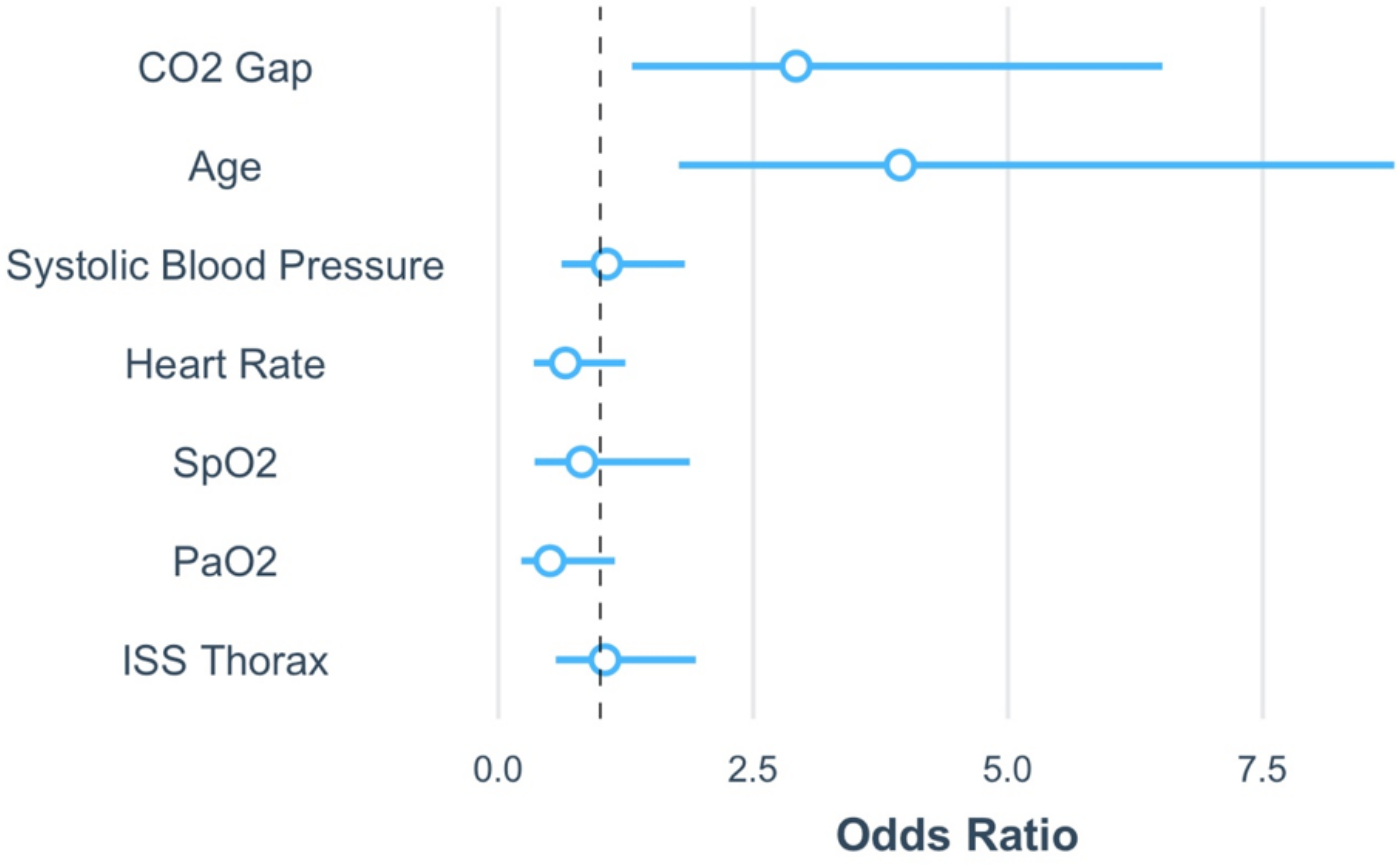

Figure 4

Scaled regression coefficient of the multivariate logistic regression. Footnote: Illustration of the multivariate logistic regression model summarized on Table 3. Regression coefficients are exponentiated and scaled. The horizontal lines around the dots indicates the 95% confidence interval of the odds ratio. CO2 gap = PaO2 - EtCO2.