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Impact of mild hypercapnia in critically ill patients with metabolic acidosis

Ary Serpa Neto [a,b,c,d], Ahmad Nasser [e,f], Prashanti Marella [f,g], Tomoko Fujii [h], Kazunari Takahashi [h], Kevin Laupland [i,j], Alexis Tabah [f,i,k], Antony G. Attokaran [f,l], Aashish Kumar [m], James McCullough [n,o], Kiran Shekar [f,p], Peter Garrett [l,q], Sebastiaan Blank [r], Siva Senthuran [s,t], Stephen Luke [s,u], Mairead McNamara [a], Rinaldo Bellomo [a,b,c], Kyle White [f,i,v,*], on behalf of the Queensland Critical Care Research Network (QCCRN) and the SODa-BIC investigators[1,2]

[a] *Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), School of Public Health and Preventive Medicine, Monash University, Level 3 553 St Kilda Road, Melbourne, VIC 3004, Australia*
[b] *Department of Intensive Care, Austin Hospital, 145 Studley Rd, Heidelberg, VIC 3084, Australia*
[c] *Department of Critical Care, Melbourne Medical School, University of Melbourne, Austin Hospital, 157-159 Barry Street, Parkville, VIC 3010, Australia*
[d] *Department of Critical Care Medicine, Av. Albert Einstein, 627/701, Morumbi, São Paulo, SP 05652-900, Brazil*
[e] *Intensive Care Unit, Queen Elizabeth II Jubilee Hospital, Troughton Rd &, Kessels Rd, Coopers Plains, QLD 4108, Australia*
[f] *Faculty of Medicine, University of Queensland, Mayne Medical School, 20 Weightman St, Brisbane, QLD 4006, Australia*
[g] *Intensive Care Unit, Caboolture Hospital, 120 McKean St, Caboolture, QLD 4510, Australia*
[h] *Department of Intensive Care, Jikei University Hospital, 3 Chome-19-18 Nishishinbashi, Minato City, Tokyo 105-0003, Japan*
[i] *Queensland University of Technology (QUT), 2 George St, Brisbane, QLD 4000, Australia*
[j] *Department of Intensive Care Services, Royal Brisbane and Women's Hospital, Butterfield St, Herston, QLD 4006, Australia*
[k] *Intensive Care Unit, Redcliffe Hospital, Anzac Ave, Redcliffe, 4020 Brisbane, QLD, Australia*
[l] *Intensive Care Unit, Rockhampton Hospital, 2 Canning St, Rockhampton, QLD 4700, Australia*
[m] *Intensive Care Unit, Logan Hospital, Loganlea Rd, Meadowbrook, QLD 4131, Australia*
[n] *School of Medicine and Dentistry, Griffith University, Parklands Dr, Southport, QLD 4215, Australia*
[o] *Intensive Care Unit, Gold Coast University Hospital, 1 Hospital Blvd, Southport, QLD 4215, Australia*
[p] *Adult Intensive Care Services, the Prince Charles Hospital, 627 Rode Rd, Chermside, QLD 4032, Australia*
[q] *Intensive Care Unit, Sunshine Coast University Hospital, 6 Doherty St, Birtinya, QLD 4575, Australia*
[r] *Intensive Care Unit, Cairns Hospital, 165 The Esplanade, QLD, Cairns 4870, Australia*
[s] *College of Medicine and Dentistry, James Cook University, 373 Flinders St, Townsville, QLD 4810, Australia*
[t] *Intensive Care Unit, Townsville Hospital, 100 Angus Smith Dr, Douglas, QLD, Townsville 4814, Australia*
[u] *Intensive Care Services, Mackay Base Hospital, 475 Bridge Rd, Mackay, QLD 4740, Australia*
[v] *Intensive Care Unit, Princess Alexandra Hospital, 199 Ipswich Rd, Woolloongabba, QLD 4102, Australia*

* Corresponding author at: Intensive Care Unit, Princess Alexandra Hospital, 199 Ipswich Rd, Woolloongabba, QLD 4102, Australia.
E-mail address: kyle.white@health.qld.gov.au (K. White).

[1] **Collaborators - Queensland Critical Care Research Network Group.** Mahesh Ramanan, Prashanti Marella, Patrick Young, Philippa McIlroy, Sebastiaan Blank, Ben Nash, James McCullough, Kerina J Denny, Mandy Tallott, Andrea Marshall, David Moore, Sunil Sane, Aashish Kumar, Lynette Morrison, Pam Dipplesman, Jennifer Taylor, Stephen Luke, Anni Paasilahti, Ray Asimus, Jennifer Taylor, Kyle White, Jason Meyer, Rod Hurford, Meg Harward, James Walsham, Neeraj Bhadange, Wayne Stevens, Kevin Plumpton, Sainath Raman, Andrew Barlow, Alexis Tabah, Hamish Pollock, Kylie Jacobs, Antony G. Attokaran, David Austin, Jacobus Poggenpoel, Josephine Reoch, Kevin B. Laupland, Felicity Edwards, Tess Evans, Jayesh Dhanani, Marianne Kirrane, Pierre Clement, Nermin Karamujic, Paula Lister, Vikram Masurkar, Lauren Murray, Jane Brailsford, Todd Erbacher, Kiran Shekar, Jayshree Lavana, George Cornmell, Siva Senthuran, Stephen Whebell, Michelle Gatton, Sam Keogh.

[2] **Collaborators - SODa-BIC investigators.** Ary Serpa Neto, Kyle White, Tomoko Fujii, Mairead McNamara, Toby Betteridge, Shailesh Bihari, Kyle Brooks, Lewis Campbell, Khaled El-Khawas, Craig French, Atul Gaur, Rajendra Goud, Sachin Gupta, Alisa Higgins, Carol Hodgson, Umesh Kadam, Anne Leditschke, Airton Leonardo Manoel, Colin McArthur, Shay McGuinness, Elissa Milford, Priya Nair, Ahmad Nasser, Alistair Nichol, Leo Nunnink, Leanlove Navarra, Sandra Peake, Samara Pandhem, Mark Plummer, Claire Seiffert, Emily See, Paul Secombe, Ravi Tiruvoipati, Ramprasad Vegunta, Meredith Young, Fernando Zampieri, Jamie Cooper, Paul Young, Andrew Udy, Rinaldo Bellomo.

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ABSTRACT

Purpose: Clinical trials focusing on critically ill patients with metabolic acidosis, a common exclusion criterion is the presence of a $PaCO_2 > 45$ mmHg. The aim of this study was to assess the impact of mild hypercapnia on patient characteristics, severity, and clinical outcomes in critically ill patients with metabolic acidosis.

Material and methods: Multicentre, retrospective, observational study conducted in 12 intensive care units (ICUs) in Queensland, Australia. Patients with metabolic acidosis and concurrent vasopressor requirement were included and the exposure of interest was the $PaCO_2$ level at the time of meeting the eligibility criteria divided in two groups: $PaCO_2 \leq 45$ mmHg and $PaCO_2$ 46–50 mmHg. Primary clinical outcome was major adverse kidney events within 30 days (MAKE30).

Results: We studied 5601 patients, with 3605 (64.4 %) in the $PaCO_2 \leq 45$ mmHg group and 1996 (35.6 %) in the $PaCO_2$ 46–50 mmHg group. The incidence of MAKE30 was lower in the $PaCO_2$ 46–50 mmHg group (29 % vs. 34 %; OR, 0.79 [95 %CI, 0.69 to 0.90]; $p < 0.001$) as was the use of renal replacement therapy, and the incidence of acute kidney injury. After adjustment for confounders, no outcome was different between the groups. The maximum fall of pH associated with an increase of 1 mmHg of $PaCO_2$ in the $PaCO_2$ 46–50 mmHg group was 0.006.

Conclusion: In patients with metabolic acidosis, after adjustment for potential confounders, mild hypercapnia does not increase the MAKE-30 rate and does not have a major impact on pH.

1. Introduction

In studies and clinical trials focusing on critically ill patients with metabolic acidosis, a common exclusion criterion is the presence of a $PaCO_2$ greater than 45 mmHg [1–13]. This criterion is implemented due to concern about the confounding effect of respiratory acidosis [14], and the belief that the exclusion of individuals with a $PaCO_2$ above 45 mmHg allows investigators to concentrate specifically on the impact of metabolic acidosis. However, the actual impact of mild hypercapnia in patients with metabolic acidosis is unknown.

Recently, an international clinical trial of bicarbonate therapy for metabolic acidosis with acidemia initiated the enrolment of patients with a $PaCO_2 < 50$ mmHg instead of 45 mmHg [15]. However, the implications of increasing the $PaCO_2$ threshold from 45 to 50 mmHg on patient characteristics, disease severity, and clinical outcomes need to be elucidated. Moreover, the relationship between incremental increases in $PaCO_2$ within this range in patients with metabolic acidosis and changes in pH remains unclear. Clarification of these issues is essential for optimizing patient selection criteria for current and future trials in the management of acidosis, especially in patients where lung-protective ventilation and permissive hypercapnia may be applied.

The aim of this study was to assess the impact of mild hypercapnia on patient characteristics, severity, MAKE30 and other clinical outcomes in critically ill patients with metabolic acidosis and to estimate the impact of $PaCO_2$ increments on pH levels. The focus was on renal outcomes because most of the available evidence on the topic suggest that metabolic acidosis (and its potential treatment with sodium bicarbonate) has more consequences in renal outcomes in this group of patients [1–3].

2. Material and methods

2.1. Study design and ethics

Multicentre, retrospective, observational study conducted in 12 intensive care units (ICUs) in Queensland, Australia. The Metro South Hospital and Health Service Human Research Ethics Committee (HREC/2022/QMS/82024) approved the study, and an individual waiver of consent was granted. According to local regulations, all sites included in the study were supported by the Metro South Hospital and Health Service Human Research Ethics Committee, resulting in one HREC approval for all sites followed by research governance approval in each site. All data is de-identified according to regulations and is in accordance with the precepts of the Declaration of Helsinki.

2.2. Data sources

Data was collected from Australian ICUs using the eCritical MetaVision™ (iMDsoft, Boston, MA, USA) clinical information systems and the Australia and New Zealand Intensive Care Society (ANZICS) CORE Adult Patient Database (APD).

2.3. Patients

All patients were eligible if their electronic medical records were retrievable. Patients were included if they: 1) were adults (≥ 18 years); 2) had metabolic acidosis in at least one blood gas during ICU stay (defined as pH < 7.30, base excess [BE] ≤ −4 mmol/L and $PaCO_2 \leq 50$ mmHg); and 3) were receiving a vasopressor infusion at the moment of diagnosis of metabolic acidosis. Patients were excluded if: 1) readmission; 2) diagnosed with advanced chronic kidney disease requiring dialysis; 3) receiving renal replacement therapy at the time of meeting eligibility criteria; 4) admitted with palliative intent; and 5) transferred from another participating ICU.

2.4. Exposure

The exposure of interest was the $PaCO_2$ level at the time of meeting the eligibility criteria. Thus, patients were divided in two groups: $PaCO_2 \leq 45$ mmHg and $PaCO_2$ 46–50 mmHg. pH, base excess, $PaCO_2$ and additional information were always collected from the same blood gas. When more than one blood gas had the eligibility criteria, the first blood gas fulfilling the criteria was used, and in all analyses, time zero was the first time that the patient met the eligibility criteria, and the maximum follow-up time was 30 days from time zero.

2.5. Outcomes

The primary outcome was major adverse kidney events within 30 days (MAKE30) of time zero defined as a composite of 30-day hospital mortality, receipt of renal replacement therapy and persistent renal dysfunction (defined as the creatinine closest to day 30 ≥ 200 % of the baseline value). This was chosen as the same primary outcome to the ongoing SODa-BIC trial [2] for which potential trial recruitment of patients with a $PaCO_2$ between 45 and 50 mmHg is relevant.

Secondary outcomes included: 1) 30-day in-hospital mortality; 2) receipt of renal replacement therapy within 30 days; 3) persistent renal dysfunction within 30 days; 4) incidence and maximum stage of acute kidney injury (AKI) within 30 days (defined using only the creatinine component of the Kidney Disease Improving Global Outcomes [KDIGO] AKI criteria) [16]; 5) ICU-free days at day 30 (defined as 30 – ICU length

of stay; non-survivors at day 30 were assigned zero); and 6) impact of $PaCO_2$ increments on pH levels.

2.6. Statistical analysis

Continuous data was reported as median (quartile 25th – quartile 75th) and compared using Wilcoxon rank-sum test. Categorical variables were reported using number and percentages and compared using Fisher exact text. The effect of the exposure group on binary outcomes, including the primary outcome, was assessed using generalized linear models with binomial distribution unadjusted for confounders and reported as odds ratio (OR) and 95 % confidence interval (CI). The impact of the exposure on ICU-free days at day 30 was assessed using cumulative logistic regression models unadjusted for confounders and reported as common odds ratio (COR) with its 95 % CI. In addition to the unadjusted analyses, adjusted analyses were performed considering sites as random effect and adjusting for the following pre-specified variables: 1) age; 2) APACHE (Acute Physiology and Chronic Health Evaluation) III score; 3) admission diagnosis; 4) use of mechanical ventilation; 5) presence of septic shock; 6) SOFA (Sequential Organ Failure Assessment); 7) baseline creatinine; and 8) use of sodium bicarbonate.

To understand the impact of $PaCO_2$ increments on pH levels, a mixed-effect generalized linear regression model was used with pH as the dependent variable and $PaCO_2$ as the independent variable. In this analysis, the unit of analysis was the blood gas and not the patient. Thus, a patient could have more than one blood gas included (if the blood gas met the eligibility criteria as described above). This analysis was performed without adjustment but including patients as random effects to account for the clustering of the data, and blood gases were matched according to base excess level and the analysis was repeated.

As a sensitivity analysis, the analyses described above were repeated considering only patients receiving invasive ventilation in the $PaCO_2$ 46–50 mmHg group. In addition, a sensitivity analyses excluding patients with diabetic ketoacidosis was performed. Only complete case analyses were performed (**eTable 1** in **Online Supplement**). All analyses were performed in R v.4.3.3 and a $p < 0.05$ was considered statistically significant. For the three components of the primary outcome, a Bonferroni correction for multiplicity was used and a $p < 0.016$ was considered significant.

3. Results

3.1. Patients

Overall, 89,494 patients were assessed for inclusion, with 6318 (7 %) fulfilling eligibility criteria. After exclusions, 5601 patients remained, with 3605 (64.4 %) in the $PaCO_2 \leq 45$ mmHg group and 1996 (35.6 %) in the $PaCO_2$ 46–50 mmHg group (**eFigure 1** in **Online Supplement**). Within the $PaCO_2$ 45–50 mmHg group, 1862 (93 %) patients were ventilated at the time of eligibility.

Patients in the $PaCO_2 \leq 45$ mmHg group were sicker, were more likely to be in septic shock, to be receiving higher doses of noradrenaline, to have lower base excess levels, and higher lactate and creatinine levels (Table 1 and **eTable 2** in **Online Supplement**). In addition, patients in the $PaCO_2 \leq 45$ mmHg group received sodium bicarbonate more often (28 % vs. 17 %; $p < 0.001$). The use of invasive ventilation, however, was more frequent in patients in the $PaCO_2$ 46–50 mmHg group.

3.2. Outcomes

The incidence of MAKE30 was lower in the $PaCO_2$ 46–50 mmHg group (29 % vs. 34 %; OR, 0.79 [95 %CI, 0.69 to 0.90]; $p < 0.001$) (Table 2 and Fig. 1) as were the use of renal replacement therapy, and the incidence of AKI. There was no difference in outcomes after adjustment for confounders. 30-day crude and mortality was similar

Table 1
– Baseline Characteristics and Use of Bicarbonate in Included Patients.

	$PaCO_2$ 46–50 mmHg ($n = 1996$)	$PaCO_2 \leq 45$ mmHg ($n = 3605$)	*p* value
Age, years	63 (51–71)	63 (50–72)	0.708
Male gender – no. (%)	1368 (68.5)	2099 (58.2)	< 0.001
Body mass index, kg/m^2	28.3 (24.7–33.2)	27.8 (24.2–32.7)	0.002
APACHE III score	68.0 (53.0–89.0)	74.0 (58.0–96.0)	< 0.001
Risk of death	0.14 (0.04–0.43)	0.20 (0.07–0.50)	< 0.001
Days between ICU admission and eligibility	1 (1–2)	1 (1–2)	0.001
Surgical patients – no. (%)	1053 (52.8)	1637 (45.4)	< 0.001
Sepsis – no. (%)	671 (33.6)	1506 (41.8)	< 0.001
Septic shock – no. (%)	413 (20.7)	1018 (28.2)	< 0.001
Diabetic ketoacidosis – no. (%)	2 (0.1)	68 (2.1)	< 0.001
Acute respiratory distress syndrome – no. (%)	8 (0.4)	8 (0.2)	0.295
Total SOFA at eligibility	12 (11–14)	13 (11–15)	0.066
Creatinine at baseline, μmol/L*	96 (74–132)	111 (81–169)	< 0.001
Co-existing disorders – no. (%)			
Chronic cardiovascular disease	50 (2.5)	73 (2.0)	0.254
Chronic respiratory disease	51 (2.6)	53 (1.5)	0.005
Diabetes	14 (1.6)	58 (3.6)	0.004
Chronic kidney disease	24 (1.2)	51 (1.4)	0.546
Metastatic cancer	40 (2.0)	84 (2.3)	0.450
Liver cirrhosis	51 (2.6)	98 (2.7)	0.795
Admission diagnosis – no. (%)			< 0.001
Cardiovascular	934 (46.8)	1328 (36.8)	
Gastrointestinal	265 (13.3)	593 (16.5)	
Respiratory	153 (7.7)	157 (4.4)	
Sepsis	222 (11.1)	574 (15.9)	
Trauma	186 (9.3)	359 (10.0)	
Other	236 (11.8)	593 (16.5)	
Organ support at eligibility			
Invasive ventilation – no. (%)	1862 (93.3)	3030 (84.0)	< 0.001
Noradrenaline dose, μg/min	6.5 (2.8–13.0)	8.7 (4.0–16.0)	< 0.001
Blood gas at eligibility			
pH	7.26 (7.22–7.28)	7.26 (7.23–7.28)	< 0.001
Base excess, mEq/L	−6.0 (−8.1 - -4.9)	−9.0 (−11.8 - -7.3)	< 0.001
$PaCO_2$, mmHg	48 (47–49)	40 (36–43)	< 0.001
Bicarbonate, mmol/L	21 (19–22)	17 (15–19)	< 0.001
Laboratory at eligibility			
Lactate, mmol/L	1.9 (1.2–3.5)	2.4 (1.3–4.8)	< 0.001
Creatinine, μmol/L	101 (77–142)	118 (84–181)	< 0.001
Urea, mmol/L	7.1 (5.2–10.9)	8.1 (5.6–12.9)	< 0.001
Use of sodium bicarbonate during follow-up			
Received sodium bicarbonate – no. (%)	339 (17.0)	1011 (28.0)	< 0.001
Total amount, mmol	100 (100–204)	150 (100–250)	0.133

Data are median (quartile 25th – quartile 75th) or number (%).
Abbreviations: APACHE is Acute physiology and chronic health evaluation; SOFA is Sequential organ failure assessment.
* First creatinine after ICU admission.

Table 2
– Clinical Outcomes.

			Unadjusted Analyses		Adjusted Analyses*	
	$PaCO_2$ 46–50 mmHg ($n = 1996$)	$PaCO_2 \leq 45$ mmHg ($n = 3605$)	Effect Estimate (95 % CI)	*p* value	Effect Estimate (95 % CI)	*p* value
Major adverse kidney events within 30 days – no. (%)	494 / 1720 (28.7)	1044 / 3091 (33.8)	OR, 0.79 (0.69 to 0.90)	< 0.001	OR, 1.07 (0.89 to 1.29)	0.447
30-day mortality – no. (%)	303 / 1879 (16.1)	586 / 3377 (17.4)	OR, 0.92 (0.79 to 1.06)	0.255	OR, 1.28 (1.04 to 1.58)	0.020
Use of renal replacement therapy – no. (%)	236 / 1996 (11.8)	518 / 3605 (14.4)	OR, 0.80 (0.68 to 0.94)	0.008	OR, 1.04 (0.82 to 1.31)	0.741
Persistent renal dysfunction[a] – no. (%)	103 / 1700 (6.1)	178 / 3013 (5.9)	OR, 1.03 (0.80 to 1.32)	0.833	OR, 1.03 (0.77 to 1.37)	0.844
Acute kidney injury within 30 days – no. (%)	741 / 1996 (37.1)	1443 / 3605 (40.0)	OR, 0.88 (0.79 to 0.99)	0.033	OR, 0.98 (0.85 to 1.13)	0.814
Stage 1	411 / 741 (55.5)	752 / 1443 (52.1)				
Stage 2	105 / 741 (14.2)	166 / 1443 (11.5)		0.011		
Stage 3	225 / 741 (30.4)	525 / 1443 (36.4)				
ICU-free days at day 30	26.0 (18.4–28.4)	25.5 (15.2–28.2)	COR, 1.16 (1.07 to 1.26)	0.002	COR, 0.95 (0.85 to 1.07)	0.415
	Invasively Ventilated $PaCO_2$ 46–50 mmHg ($n = 1862$)	**$PaCO_2 \leq 45$ mmHg ($n = 3605$)**				
Major adverse kidney events within 30 days – no. (%)	471 / 1603 (29.4)	1044 / 3091 (33.8)	OR, 0.82 (0.72 to 0.93)	0.002	OR, 1.04 (0.87 to 1.25)	0.654
30-day mortality – no. (%)	293 / 1747 (16.8)	586 / 3377 (17.4)	OR, 0.96 (0.82 to 1.12)	0.601	OR, 1.28 (1.03 to 1.58)	0.023
Use of renal replacement therapy – no. (%)	221 / 1862 (11.9)	518 / 3605 (14.4)	OR, 0.80 (0.68 to 0.95)	0.011	OR, 1.01 (0.80 to 1.28)	0.928
Persistent renal dysfunction[a] – no. (%)	101 / 1591 (6.3)	178 / 3013 (5.9)	OR, 1.08 (0.84 to 1.39)	0.551	OR, 1.00 (0.76 to 1.33)	0.974
Acute kidney injury within 30 days – no. (%)	684 / 1862 (36.7)	1443 / 3605 (40.0)	OR, 0.87 (0.77 to 0.98)	0.018	OR, 0.88 (0.76 to 1.02)	0.092
Stage 1	389 / 684 (56.9)	752 / 1443 (52.1)				
Stage 2	99 / 684 (14.5)	166 / 1443 (11.5)		0.001		
Stage 3	196 / 684 (28.7)	525 / 1443 (36.4)				
ICU-free days at day 30	25.7 (17.7–28.4)	25.5 (15.2–28.2)	COR, 1.10 (0.99 to 1.22)	0.064	COR, 0.95 (0.85 to 1.07)	0.410

Data are median (quartile 25th – quartile 75th) or number (%).
Abbreviations: ICU is intensive care unit; COR is common odds ratio; OR is odds ratio.
* Adjusted for age, APACHE III, admission diagnosis, use of mechanical ventilation, presence of septic shock, total SOFA, baseline creatinine and use of sodium bicarbonate. Sites were included as random effects.
[a] Defined as creatinine closest to day 30 ≥ 200 % of the baseline value at time zero.

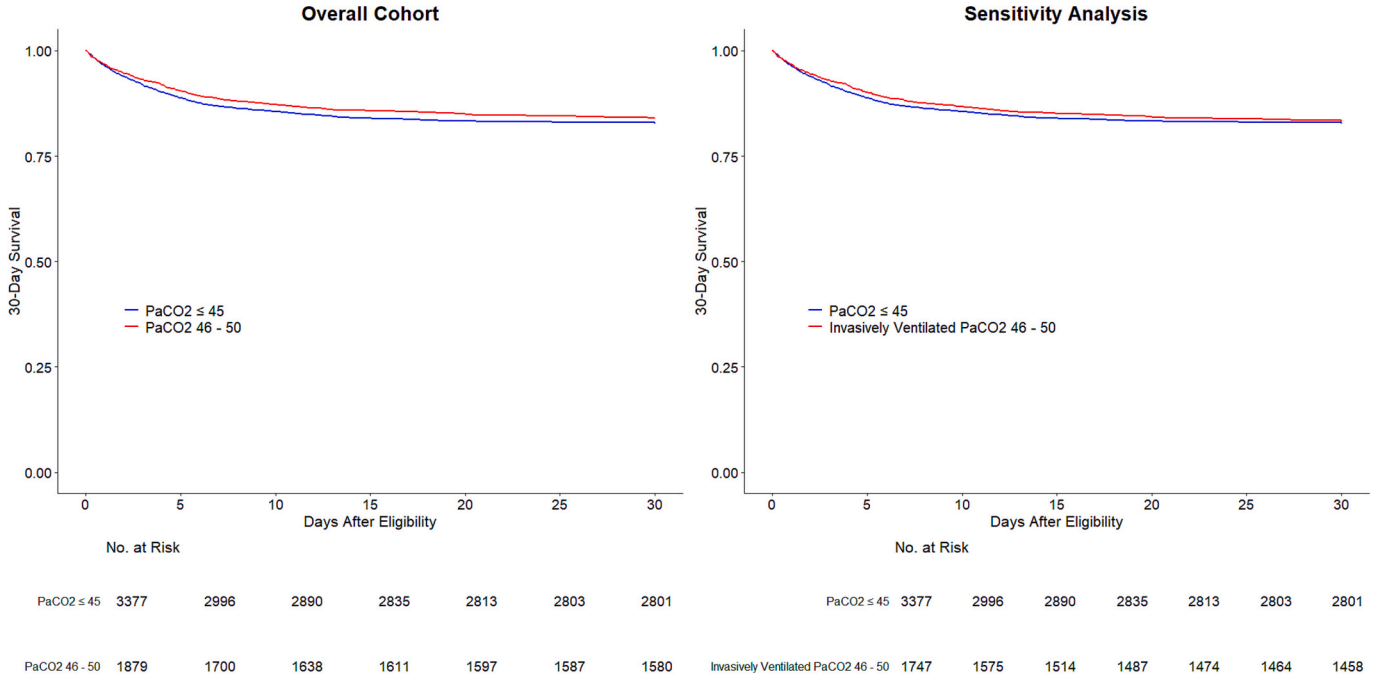

Fig. 1. –30-Day Survival According to $PaCO_2$ Groups. Kaplan-Meier curves reporting the 30-day survival according to $PaCO_2$ groups.

between the groups (16 % vs. 17 %; OR, 0.92 [95 %CI, 0.79 to 1.06]; $p = 0.255$) (Table 2).

3.3. Sensitivity analysis

Baseline characteristics when considering only invasively ventilated patients in the $PaCO_2$ 46–50 mmHg group is reported in Table 3. Clinical outcomes in this sensitivity analysis were consistent with the main analysis and are reported in Table 2 and Fig. 1. Findings from the sensitivity analysis excluding patients with diabetic ketoacidosis are reported in **eTables 3** and **4** in **Online Supplement**. Clinical outcomes in this sensitivity analysis were consistent with the main analysis.

3.4. Relationship between pH and $PaCO_2$

An increase in $PaCO_2$ level was associated with a decrease in pH in the $PaCO_2$ in both groups (Fig. 2). The maximum fall of pH associated with an increase of 1 mmHg of $PaCO_2$ in the $PaCO_2$ 46–50 mmHg group was 0.006 pH units (Fig. 2).

4. Discussion

In a multicentre study involving thousands of patients with metabolic acidosis, those with mild hypercapnia had different baseline characteristics compared to those without mild hypercapnia, most notably a lower severity of illness and greater use of invasive ventilation. In such mildly hypercapnic patients, the primary outcome of MAKE30 was lower as were the use of renal replacement therapy, and the incidence of AKI. However, after adjustment, most of the outcomes were similar between groups, although the risk of 30-day mortality was higher in the mild hypercapnia group. All results were consistent when assessing only invasively ventilated patients in the mild hypercapnia group. Finally, despite a statistically significant association between increase in $PaCO_2$ levels and decrease in pH levels in the mild hypercapnia group, the magnitude of such change was small.

4.1. Relationship to previous studies

The largest clinical trial in this field randomised only patients with $PaCO_2 < 45$ mmHg, following seminal papers on acid-base derangements [1]. Similar to this, an ongoing trial (BICARICU-2) is only randomising patients with $PaCO_2 < 45$ mmHg [5]. In both trials, the enrolment criteria mentioned only exclusion of patients with pure respiratory acidosis (defined by pH $\leq$ 7.20, $PaCO_2 > 50$ mmHg and bicarbonate equal or greater than ($PaCO_2$–40) / 10 + 24) or patients with $PaCO_2 > 45$ mmHg and spontaneous breathing [1,5]. Overall, there is no mention of mild hypercapnia in patients receiving mechanical ventilation. Another ongoing clinical trial is randomising patients with $PaCO_2 < 50$ mmHg independently of ventilation status but no further justification or evidence for this choice is provided [15].

4.2. Implications of study findings

The present findings suggest that, despite changes in baseline characteristics, the cohort of invasively ventilated patients with mild hypercapnia and metabolic acidosis have a lower unadjusted MAKE30 score. Moreover, patients with mild hypercapnia had a similar adjusted MAKE30 and other renal outcomes to patients without mild hypercapnia after adjustment for confounders. The inclusion of this group of patients in future studies, therefore, can help boost recruitment, without markedly distorting the risk of primary and secondary outcomes and facilitate the adoption of lung-protective ventilation and permissive hypercapnia. In addition, a slightly lower MAKE-30 rate and a similar mortality rate between the groups suggests that the inclusion of this group in unlikely to jeopardize trial integrity or result in a lower number of events.

Table 3
– Baseline Characteristics and Use of Bicarbonate in Included Patients Considering Only Invasively Ventilated Patients in the $PaCO_2$ 46–50 mmHg Group.

	Invasively Ventilated $PaCO_2$ 46–50 mmHg ($n = 1862$)	$PaCO_2 \leq 45$ mmHg ($n = 3605$)	*p* value
Age, years	63.0 (51.0–71.0)	63.0 (50.0–72.0)	0.870
Male gender – no. (%)	1299 (69.8)	2099 (58.2)	< 0.001
Body mass index, kg/m^2	28.2 (24.7–33.1)	27.8 (24.2–32.7)	0.010
APACHE III score	69.0 (53.0–90.0)	74.0 (58.0–96.0)	< 0.001
Risk of death	0.1 (0.0–0.5)	0.20 (0.07–0.50)	< 0.001
Days between ICU admission and eligibility	1.0 (1.0–2.0)	1 (1–2)	0.017
Surgical patients – no. (%)	985 (52.9)	1637 (45.4)	< 0.001
Sepsis – no. (%)	616 (33.1)	1506 (41.8)	< 0.001
Septic shock – no. (%)	389 (20.9)	1018 (28.2)	< 0.001
Diabetic ketoacidosis – no. (%)	1 (0.1)	68 (2.1)	< 0.001
Acute respiratory distress syndrome – no. (%)	8 (0.5)	8 (0.2)	0.192
Total SOFA at eligibility	13 (11–14)	13 (11–15)	0.953
Creatinine at baseline, µmol/L	96 (74–131)	111 (81–169)	< 0.001
Admission diagnosis – no. (%)			< 0.001
Cardiovascular	897 (48.2)	1328 (36.8)	
Gastrointestinal	244 (13.1)	593 (16.5)	
Gynaecological	7 (0.4)	30 (0.8)	
Haematological	5 (0.3)	7 (0.2)	
Metabolic	56 (3.0)	208 (5.8)	
Musculoskeletal / Skin	45 (2.4)	72 (2.0)	
Neurological	69 (3.7)	159 (4.4)	
Renal / Genitourinary	31 (1.7)	116 (3.2)	
Respiratory	148 (7.9)	157 (4.4)	
Sepsis	178 (9.6)	574 (15.9)	
Trauma	182 (9.8)	359 (10.0)	
Other	0 (0.0)	1 (0.0)	
Organ support at eligibility			
Invasive ventilation – no. (%)	1862 (100.0)	3030 (84.0)	< 0.001
Noradrenaline dose, µg/min	6.8 (2.8–13.3)	8.7 (4.0–16.0)	< 0.001
Blood gas at eligibility			
pH	7.26 (7.22–7.28)	7.26 (7.23–7.28)	< 0.001
Base excess, mEq/L	−6.0 (−8.2 - -4.9)	−9.0 (−11.8 - -7.3)	< 0.001
$PaCO_2$, mmHg	48 (47–49)	40 (36–43)	< 0.001
Bicarbonate, mmol/L	21 (19–22)	17 (15–19)	< 0.001
Laboratory ate eligibility			
Lactate, mmol/L	1.9 (1.2–3.5)	2.4 (1.3–4.8)	< 0.001
Creatinine, µmol/L	100 (76–140)	118 (84–181)	< 0.001
Urea, mmol/L	7.0 (5.2–10.5)	8.1 (5.6–12.9)	< 0.001
Sodium, mmol/L	138 (136–140)	138 (135–140)	0.035
Potassium, mmol/L	4.8 (4.3–5.2)	4.7 (4.3–5.3)	0.050
Chloride, mmol/L	108 (105–110)	108 (105–112)	< 0.001
Use of sodium bicarbonate during follow-up			
Received sodium bicarbonate – no. (%)	325 (17.5)	1011 (28.0)	< 0.001
Days until first dose	0.0 (0.0–1.0)	0 (0–1)	0.099

(*continued on next page*)

Table 3 (*continued*)

	Invasively Ventilated $PaCO_2$ 46–50 mmHg ($n = 1862$)	$PaCO_2 \leq 45$ mmHg ($n = 3605$)	*p* value
Number of doses	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.007
Total amount, mmol	100 (100–219)	150 (100–250)	0.141
Mean amount, mmol	100 (100–200)	100 (100–200)	0.977
Lowest amount, mmol	100 (100–181)	100 (100–150)	0.108
Highest amount, mmol	100 (100–200)	100 (100–200)	0.460
Type of sodium bicarbonate – no. (%)			
8.4 % sodium bicarbonate	303 (16.3)	929 (25.8)	< 0.001
Isotonic bicarbonate	27 (1.5)	101 (2.8)	0.002

Data are median (quartile 25th – quartile 75th) or number (%).
Abbreviations: APACHE is Acute physiology and chronic health evaluation; SOFA is Sequential organ failure assessment.

4.3. Strengths and limitations

The present study included a large cohort with a wide array of ICU admissions as the included ICUs encompass the full range of adult critical care services except for acute heart and lung transplants. The data collected was validated, and complete. Moreover, given its collection by non-research staff, it represents a non-biased sample. Furthermore, the study population was remarkably similar to a recent trial in the field [2].

The present study has limitations. Given the observational design, causality may not be implied. The heterogeneity of the study population, with unknown medical comorbidities and a wide range of admission diagnoses, may have potentially influenced outcomes. Further exploration of subgroups within the study population will be required to assess within population differences in outcomes and findings. Only patients receiving vasopressors were included and the findings observed in the study should be restricted to this population. Also, chronic carbon dioxide retainers were not excluded from the sample, and the impact of mild hypercapnia is potentially different in this subgroup. No data on ventilation parameters, including tidal volume, is available limiting the assessment of the impact of ventilation strategy on the findings of the present study. It is important to highlight that the evaluation of outcomes between the $PaCO_2$ groups is speculative, since the groups are unbalanced especially in the severity of illness. Also, no respiratory acidosis compensation equations were used to identify eligible patients. Only the information from the first blood gas fulfilling eligibility criteria was used in the study, to mimic the time zero of a clinical trial. However, the impact of persistent acidosis is potentially different from brief periods of acidosis and this was not assessed in the present study as this was not the initial objective. Finally, almost 15 % of the patients were lost to follow-up for the primary outcome of MAKE30 and this should be interpreted with cautious.

5. Conclusions

Patients with mild hypercapnia and metabolic acidosis had different baseline characteristics compared to patients with metabolic acidosis without mild hypercapnia, mainly a lower severity of illness, and greater use of invasive ventilation. However, unadjusted MAKE-30 was slight lower than in patients without hypercapnia. Moreover, while mortality was similar in the groups, all other secondary outcomes were better in the mild hypercapnia group in unadjusted analyses. In addition, after adjustment, MAKE-30 rates were not significantly different, and all adjusted secondary outcomes were similar. The decrease in pH in the mild hypercapnia group was also small and appeared of limited clinical relevance. The present findings suggest that recruitment of patients with a $PaCO_2$ between 45 and 50 mmHg in trials of metabolic acidosis is acceptable. However, as patients with metabolic acidosis and mild hypercapnia are less severe, caution should be considered as this may influence future studies that tolerate it as an inclusion criterion.

CRediT authorship contribution statement

Ary Serpa Neto: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ahmad Nasser:** Writing – review & editing, Validation, Conceptualization. **Prashanti Marella:** Writing – review & editing, Validation, Conceptualization. **Tomoko Fujii:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Kazunari Takahashi:** Writing – review & editing, Validation, Conceptualization. **Kevin Laupland:** Writing – review & editing, Validation, Conceptualization. **Alexis Tabah:** Writing – review & editing, Validation, Conceptualization. **Antony G. Attokaran:** Writing – review & editing, Validation, Conceptualization. **Aashish Kumar:** Writing – review & editing, Validation, Conceptualization. **James McCullough:** Writing – review & editing, Validation, Conceptualization. **Kiran Shekar:** Writing – review & editing, Validation, Conceptualization. **Peter Garrett:** Writing – review & editing, Validation, Conceptualization. **Sebastiaan Blank:** Writing – review & editing, Validation, Conceptualization. **Siva Senthuran:** Writing – review & editing, Validation, Conceptualization. **Stephen Luke:** Writing – review & editing, Validation, Conceptualization. **Mairead McNamara:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Rinaldo Bellomo:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Kyle White:** Writing – review & editing, Writing – original draft, Validation, Project

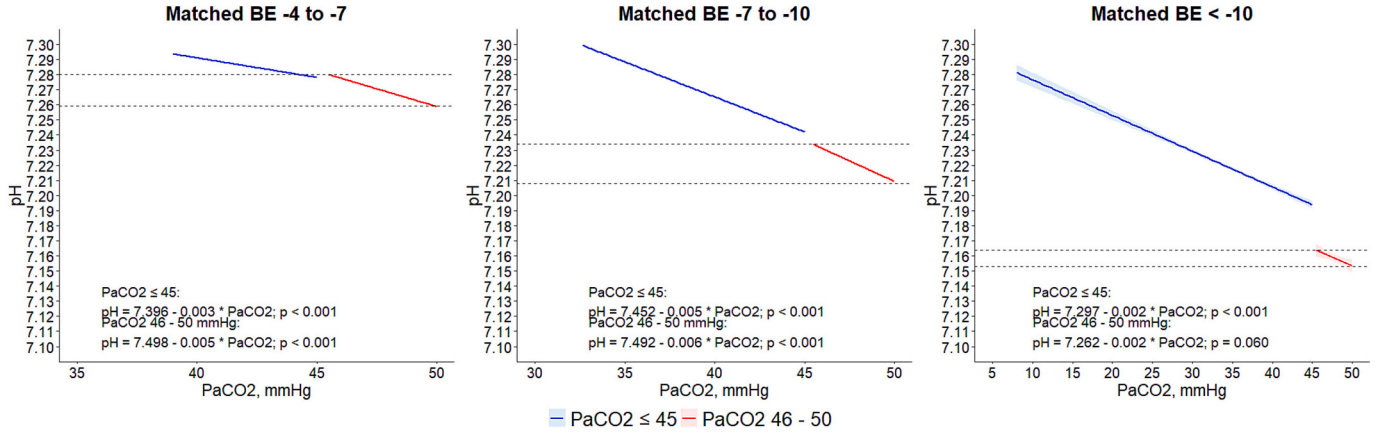

Fig. 2. – Changes in pH Levels According to $PaCO_2$ Levels. Dashed lines represent the maximum range of pH in the $PaCO_2$ 46–50 mmHg group.

administration, Methodology, Formal analysis, Data curation, Conceptualization.

Data availability

Data cannot be shared publicly due to institutional ethics, privacy, and confidentiality regulations. Data released for the purposes of research under section 280 of the Public Health Act 2005 requires an application to the Director-General of Queensland Health (PHA@health.qld.gov.au).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2024.154936.

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