Early metabolic acidosis in critically ill patients: a binational multicentre study

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Metabolic acidosis (MA) is a major physiological derangement associated with mortality.[1] There is no specific treatment for MA, beyond treating its cause. However, the administration of buffering solutions to correct MA may be common practice in the intensive care unit (ICU). The rationale for such therapy is that, independent of its cause, MA with acidaemia impairs the performance of the cardiovascular system[2,3] and should be corrected. To reduce this perceived cardiovascular dysfunction, sodium bicarbonate is the most commonly used agent.[4,5] However, until recently there have been little or no data on its effectiveness.[6,7]

In 2018, Jaber and colleagues[8] reported the findings of a multicentre, open-label, randomised controlled trial of the efficacy of intravenous sodium bicarbonate for critically ill patients with severe MA (BICAR-ICU trial). The trial investigators found that the administration of sodium bicarbonate reduced the use of renal replacement therapy (RRT) in the ICU, and decreased 28-day mortality in the subgroup of patients with acute kidney injury Stage 2 and 3. These findings have created renewed interest in the use of sodium bicarbonate for MA.

However, it is unclear how many patients such an intervention would apply to and what the outcome of such patients in the setting of usual care might be. Moreover, for the purpose of designing and powering a trial, it is unknown whether investigators should apply more moderate criteria for MA to achieve more efficient patient selection. In particular, patients with moderate MA may also have a high mortality risk and a much greater prevalence than severe MA. This larger population would then enable the conduct of a trial with greater external validity and with recruitment that is more efficient.

Accordingly, the aim of the study was to measure the incidence, prevalence, characteristics and outcomes of patients with both severe MA (using the BICAR-ICU trial criteria) and moderate MA (using new criteria) in Australian and New Zealand ICUs.

ABSTRACT

Objective: We aimed to measure the incidence, prevalence, characteristics and outcomes of intensive care unit (ICU) patients with early (first 24 hours) metabolic acidosis (MA) according to two different levels of severity with a focus on recent data.

Design: We retrospectively applied two diagnostic criteria to our analysis based on literature for early MA: i) severe MA criteria (pH ≤ 7.20 and $Paco_2$ ≤ 45 mmHg and HCO_3^- ≤ 20 mmol/L with total Sequential Organ Failure Assessment [SOFA] score ≥ 4 or lactate ≥ 2 mmol/L), and ii) moderate MA criteria (pH < 7.30 and base excess < –4 mmol/L and $Paco_2$ ≤ 45 mmHg).

Setting: ICUs in the Australian and New Zealand Intensive Care Society Adult Patient Database program.

Participants: Adult patients registered to the database from 2008 to 2018.

Main outcome measures: Incidence, prevalence, and hospital mortality of patients with MA by the two criteria.

Results: We screened 1 076 087 patients. Given the Australian and New Zealand population during the study period, we estimated the incidence of severe MA at 39.5 per million per year versus 349.2–411.5 per million per year for moderate MA. In the most recent 2 years, we observed early severe MA in 1.5% (1350/87 110) of patients compared with 8.4% (20 679/244 740) for moderate MA. Overall, hospital mortality for patients with early severe MA was 48.3% (652/1350) compared with 21.5% (4444/20 679) for moderate MA.

Conclusions: Early severe MA is uncommon in Australian and New Zealand ICUs and carries a very high mortality. Moderate MA is over seven-fold more common and still carries a high mortality.

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Methods

Study design, setting and population

We conducted a retrospective cohort study using the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD). The ANZICS-APD is a high quality binational database that encompasses more than 90% (n = 193) of all ICUs in both countries.

We screened admission records of these 193 ICUs from January 2008 through to December 2018. We excluded the following admissions: ICU admission for palliative end-of-life care or purpose of organ donation, readmission to the ICU in the same hospital stay, pH and arterial partial pressure of carbon dioxide ($Paco_2$) not measured simultaneously, base excess suggestive of data errors (< –30 mmol/L or > 30 mmol/L), and missing data for outcome at hospital discharge.

The Alfred Health Ethics Committee, Melbourne, Australia, approved the study protocol (No. 775/19).

Data collection

Variables included baseline characteristics, laboratory data and urine output on ICU admission day and treatments during the ICU stay of patients. In addition, the database contains ICU and hospital admission data and data on survival outcomes at ICU and hospital discharge.

2017–2018 period and impact of changes on data collection

The collection methodology for blood gas analysis (BGA) data in the ANZICS-APD was changed in 2016 (Online Appendix). The system change was considered likely to cause a reduction in the recorded incidence and prevalence of acidosis compared with the previous period or the true rates. Thus, we treated the period from 2008 to 2016 and the period from 2017 to 2018 as separate and non-comparable periods. Moreover, the criteria for BICAR-ICU-type MA were studied in 2017 and 2018 because of lack of complete relevant data on lactate in the 2008–2016 period. Therefore, all comparisons between the two criteria were performed in this latter period. However, we were able to report the incidence and prevalence of moderate MA separately for the two periods.

Diagnostic criteria for metabolic acidosis

The following criteria were used to identify patients with early MA.

All laboratory data collected in the ANZICS-APD were obtained during the first 24 hours in the ICU, and the BGA data were selected to deliver the values producing the highest score for the Acute Physiology and Chronic Health Evaluation (APACHE) III-j prognostic system (Online Appendix).

BICAR-ICU criteria set No. 1 (early severe MA criteria):

- pH ≤ 7.20 AND,
- $Paco_2$ ≤ 45 mmHg AND,
- HCO_3^- ≤ 20 mmol/L AND,
- total Sequential Organ Failure Assessment (SOFA) score ≥ 4 OR lactate ≥ 2 mmol/L.

Novel ANZICS Criteria set No. 2 (moderate early MA criteria):

- pH < 7.30 AND,
- base excess < –4 mmol/L AND,
- $Paco_2$ ≤ 45 mmHg on the 24 hours after ICU admission.

Outcome measures

The primary outcome measure was hospital mortality. Secondary outcomes were ICU mortality, RRT initiation in the ICU, ICU length of stay, and hospital length of stay.

Statistical analysis

Incidence, prevalence, patient characteristics and the outcomes of patients with MA by the two criteria were summarised using descriptive statistics. Group comparisons were performed using χ^2 or Fisher exact test for categorical variables, Student t test for normally distributed data and Wilcoxon rank sum test otherwise, with results presented as number (percentage), mean (standard deviation) and median (interquartile range) respectively. Diagnostic accuracy of the two criteria for hospital mortality was determined by calculating sensitivity, specificity, positive predictive value, and negative predictive value.

To evaluate whether MA diagnosed by the two criteria was an independent predictor of mortality, hierarchical logistic regression models were fitted adjusting for key factors. These factors included APACHE III-j score without the acidosis component, sex, chronic conditions, planned ICU admission, limitations of treatment orders at the ICU admission, ICU diagnosis categories of APACHE III-j, medical or surgical, potassium and $Paco_2$, with patients nested within sites and sites treated as a random effect.

We further explored incidence and prevalence of patients with MA, as well as hospital mortality of patients with and without MA stratified by year. To investigate the change in hospital mortality over time by moderate MA, logistic regression models were fitted with main effects for year of admission, MA along with their two-way interaction and adjusting for APACHE III-j risk of death, with ICU site treated as a random effect.

We further explored patient characteristics and outcomes in patients with MA diagnosed by both criteria

after excluding chronic renal failure, ketoacidosis, and possible exogenous acidosis (patients with overdose) so as to simulate the patient screening in the BICAR-ICU trial in Australian and New Zealand ICUs.

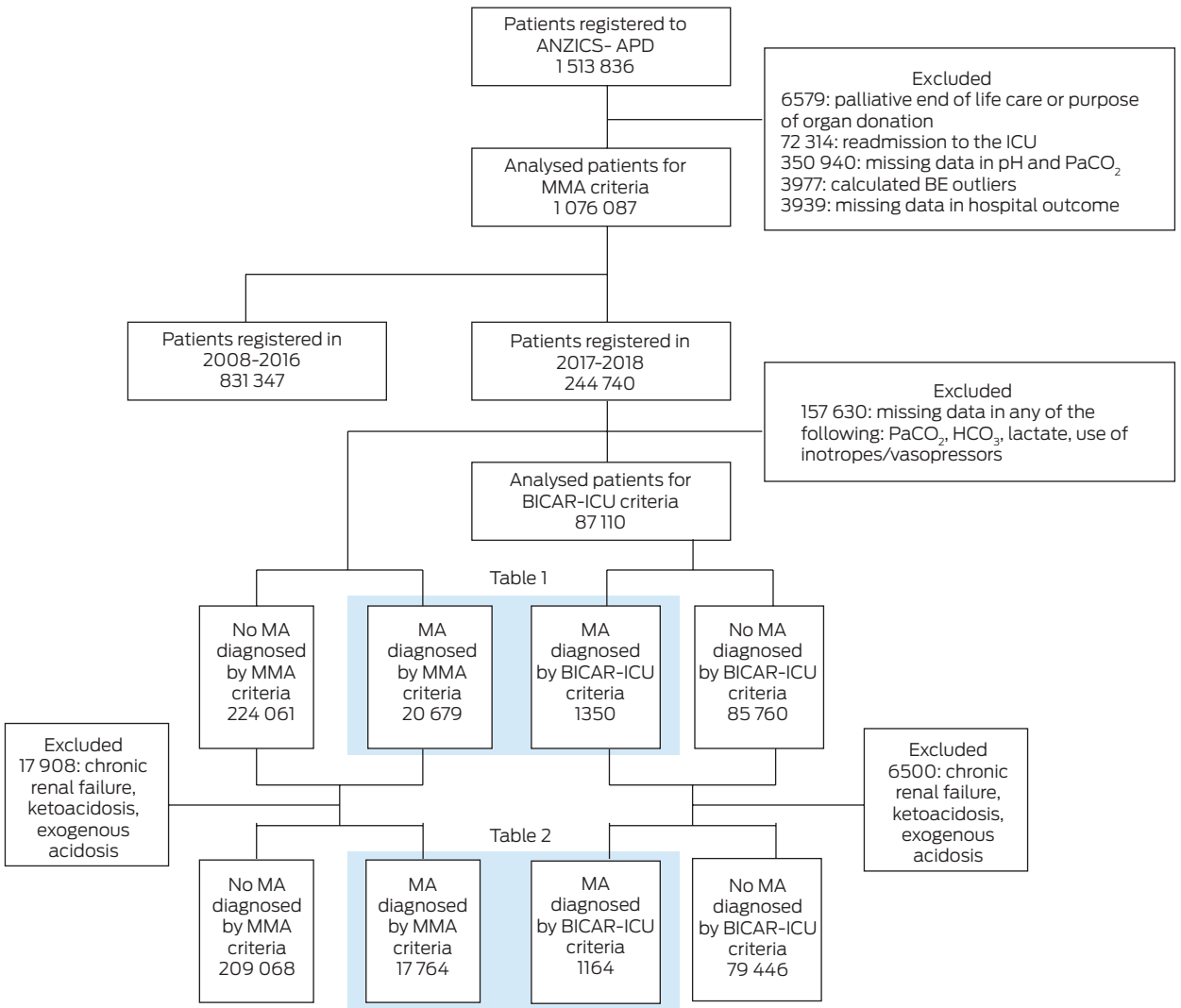
We did not impute any missing values and all available data were analysed. We performed all analyses using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria.) or SAS software version 9.4 (SAS Institute, Cary, NC, USA). Given the magnitude of the dataset, in order to more closely align statistical and clinical significance, a two-sided *P* value of 0.01 was chosen to indicate statistical significance.

Results

Patient characteristics

Among the 1 513 836 ICU admissions registered in the ANZICS-APD, 437 749 records met the pre-set exclusion criteria, leaving 1 076 087 patients for analysis (Figure 1). Of these, 244 740 were admitted to the ICU from 2017 to 2018. In this period, patients with MA by the BICAR-ICU criteria accounted only for 1.5% (1350/87 110; 157 630 patients were excluded due to missing data) of the patients in the ICU, whereas 8.4% (20 679/244 740) of patients had at least moderate MA ($P < 0.001$).

Figure 1. Study flowchart



ANZICS-APD = Australian and New Zealand Intensive Care Society Adult Patient Database; BE = base excess; BICAR-ICU = Sodium Bicarbonate to Treat Severe Acidosis in the Critically Ill: a multiple centre randomised clinical trial; HCO_3^- = bicarbonate; ICU = intensive care unit; MA = metabolic acidosis; MMA = moderate metabolic acidosis; $Paco_2$ = arterial partial pressure of carbon dioxide. The numbers of patients are indicated in each box.

Table 1. Patient characteristics, treatments, and outcomes of the study population

	Overall	BICAR-ICU severe acidosis	Moderate metabolic acidosis	*P*
Number of patients	244 740	1350/87 110* (1.5%)	20 679/244 740 (8.4%)	< 0.001
Age (years), mean (SD)	62.8 ± 17.0	62.7 ± 16.7	62.1 ± 17.4	0.16
Sex				0.56
Male	142 438 (58.2%)	732 (54.2%)	11 529 (55.8%)	
Female	102 171 (41.7%)	618 (45.8%)	9142 (44.2%)	
Other/unknown	131 (0.1%)	0 (0%)	8 (< 0.1%)	
BMI (kg/m^2), median (IQR)	27.7 (24.2–32.5)	27.7 (24.3–32.5)	27.6 (24.0–32.1)	0.26
Cardiac arrest before ICU admission	7442/236 109 (3.2%)	259/1344 (19.3%)	1708/19 540 (8.7%)	< 0.001
APACHE III-j risk of death, mean (SD)	0.141 ± 0.199	0.544 ± 0.307	0.298 ± 0.293	< 0.001
APACHE III-j: five most common ICU diagnostic codes				
1	19 723 (8.1%)†	222 (16.4%)‡	1597 (7.7%)§	
2	11 662 (4.8%)¶	208 (15.4%)**	1575 (7.6%)††	
3	11 525 (4.7%)‡‡	74 (5.5%)§§	1484 (7.2%)¶¶	
4	11 267 (4.6%)***	69 (5.1%)†††	1124 (5.4%)‡‡‡	
5	9238 (3.8%)§§§	53 (3.9%)¶¶¶	917 (4.4%)****	
SOFA score, median (IQR)	4 (2–6)	9 (6–12)	6 (3–8)	< 0.001
Surgical	144 275 (59.0%)	334 (24.7%)	8771 (42.4%)	< 0.001
Diabetic ketoacidosis	2665 (1.1%)	74 (5.5%)	1124 (5.4%)	0.99
AKI (Stage 2 or 3)	38 562 (15.8%)	759 (56.2%)	6819 (33.0%)	< 0.001
Septic shock	10 531 (4.3%)	247 (18.3%)	1886 (9.1%)	< 0.001
pH, median (IQR)	7.37 (7.31–7.41)	7.15 (7.08–7.18)	7.26 (7.19–7.28)	< 0.001
$Paco_2$ (mmHg), median (IQR)	40 (35–46)	37 (31–42)	39 (33–42)	< 0.001
Bicarbonate (lowest) (mmol/L), median (IQR)	22 (20–24)	12 (9–15)	17 (13–20)	< 0.001
Base excess (mmol/L), median (IQR)	–2.4 (–5.4 to 0.2)	–17.2 (–21.0 to –14.4)	–11.2 (–15.3 to –8.5)	< 0.001
Lactate (mmol/L), median (IQR)	1.6 (1.0–2.5)	7.0 (3.0–11.8)	2.9 (1.4–6.1)	< 0.001
Potassium (highest) (mmol/L), median (IQR)	4.4 (4.1–4.8)	5.0 (4.5–5.8)	4.8 (4.3–5.4)	< 0.001
Creatinine (highest) (μmol/L), median (IQR)	84 (65–119)	198 (132–311)	132 (85–235)	< 0.001
Mechanical ventilation	111 837/241 186 (46.4%)	1115 (82.6%)	13 305/20 418 (65.2%)	< 0.001
ECMO	479/99 675 (0.5%)	32/1260 (2.5%)	118/6027 (2.0%)	0.23
RRT	6119/101 483 (6.0%)	519/1251 (41.5%)	1857/6758 (27.5%)	< 0.001
Inotropes/vasopressor	45 727/105 450 (43.4%)	1098 (81.3%)	4873/7074 (68.9%)	< 0.001
Hospital mortality	20 484 (8.4%)	652 (48.3%)	4444 (21.5%)	< 0.001

(*continues*)

Table 1. Patient characteristics, treatments, and outcomes of the study population (*continued*)

	Overall	BICAR-ICU severe acidosis	Moderate metabolic acidosis	*P*
ICU mortality	13 584/244 263 (5.6%)	587/1348 (43.5%)	3583/20 653 (17.3%)	< 0.001
RRT initiation	4888/97 669 (5.0%)	468/1170 (40.0%)	1637/6287 (26.0%)	< 0.001
Hospital length of stay (days), median (IQR)	8.8 (5.1–15.2)	7.6 (2.1–18.9)	9.3 (4.7–17.8)	< 0.001
ICU length of stay (days), median (IQR)	1.8 (0.9–3.6)	2.8 (1.0–6.8)	2.6 (1.2–5.1)	0.28

AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; BICAR-ICU = Sodium Bicarbonate to Treat Severe Acidosis in the Critically Ill: a multiple centre randomised clinical trial; BMI = body mass index; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; $Paco_2$ = arterial partial pressure of carbon dioxide; RRT = renal replacement therapy; SD = standard deviation; SOFA = Sequential Organ Failure Assessment. * 157 630 patients excluded due to missing data. † #1207: Coronary artery bypass grafts. ‡ #503: Sepsis with shock (other than urinary). § #1207: Coronary artery bypass grafts. ¶ #1405: Gastrointestinal neoplasm. ** #102: Cardiac arrest. †† #503: Sepsis with shock (other than urinary). ‡‡ #1206: Valvular heart surgery. §§ #702: Diabetic ketoacidosis. ¶¶ #102: Cardiac arrest. *** #1902: Orthopaedic surgery. ††† #101: Cardiogenic shock. ‡‡‡ #702: Diabetic ketoacidosis. §§§ #1408: Other Gastrointestinal diseases. ¶¶¶ #901: Renal disorders. **** #1206: Valvular heart surgery.

Table 1 shows the characteristics, the interventions provided in ICU, and the outcomes of all patients and of patients with MA according to the two sets of criteria. Hypercapnia of $Paco_2$ > 45 mmHg was observed in 25.3% (61 967/244 740) of all patients. In addition, the rates of the hypercapnia were 54.6% (24 859/45 538) and 56.2% (6754/12 024) of patients, with pH < 7.30 and < 7.20 respectively. According to protocol, such patients were excluded.

Patients with MA by either criterion had higher mortality than those without MA. Hospital mortality was higher in patients with MA diagnosed by the BICAR-ICU criteria than moderate MA criteria ($P < 0.001$). Sensitivity, specificity, positive predictive value, and negative predictive value for hospital mortality of the BICAR-ICU criteria and moderate MA criteria were 8.4%, 99.1%, 48.3%, 91.7% and 21.7%, 92.8%, 21.5%, 92.8% respectively. Logistic regression analyses revealed that early MA by both criteria was independently associated with hospital mortality (early severe MA: adjusted odds ratio [aOR], 2.431; 95% CI, 2.098–2.817; $P < 0.001$; early moderate MA: aOR, 1.542; 95% CI, 1.464–1.623; $P < 0.001$).

Table 2 shows the characteristics and outcomes of patients who met the eligibility criteria of the BICAR-ICU trial, after excluding end stage renal failure, ketoacidosis, and possible exogenous toxin acidosis. These patients were compared with patients with moderate MA after excluding these conditions.

Changes in the annual incidence and prevalence of moderate MA are shown in Figure 2. For moderate MA, the average incidence rates during the period from 2008 to 2016 and the period from 2017 to 2018 were 411.5 per million per year and 349.2 per million per year respectively. While for early severe MA, the incidence was 39.5 per million per year in 2018. Annual unadjusted hospital mortality of patients with and without moderate MA as well as adjusted annual odds ratio for the hospital mortality are shown in Figure 3. The *P* value for interaction effect between moderate MA and year of admission was 0.016 for the period 2008 to 2016; however, the *P* value was 0.78 in the latter period from 2017 to 2018.

Discussion

Key findings

Using the ANZICS-APD, we found that the diagnostic criteria for MA used in the BICAR-ICU trial applied to only for 1.5% of critically ill patients, and that hospital mortality for such patients was 48.3%. In contrast, patients with moderate MA accounted for 8.4% of the Australian and New Zealand ICU population and still carried a significant hospital mortality of 21.5%. In the latest 2 years of the study period, using a different methodology for BGA inclusion, the mortality of moderate MA appeared to be increasing.

Relationship to previous studies

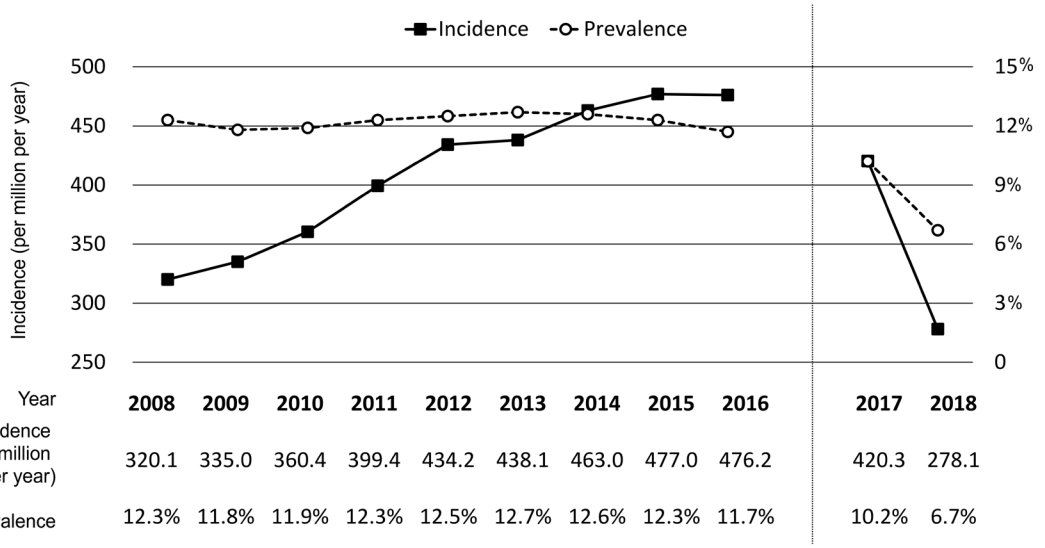
Day 28 mortality in the BICAR-ICU study was 49.1%.[8] In comparison, hospital mortality in the Australian and New Zealand ICU patients who met the eligibility criteria in the BICAR-ICU trial was 51.8%. This is despite some minor differences in the criteria applied. These findings support

Table 2. Patient characteristics and outcomes of patients who met the eligibility criteria of the BICAR-ICU cohort*

	BICAR-ICU severe acidosis	Moderate metabolic acidosis	*P*
Number of patients	1164/80 610 (1.4%)	17 764/226 832 (7.8%)	< 0.001
Age (years), mean (SD)	64.2 ± 16.0	63.9 ± 16.3	0.50
Sex			0.65
Male	643 (55.2%)	10 029 (56.5%)	
Female	521 (44.8%)	7727 (43.5%)	
Other/unknown	0 (0%)	8 (< 0.1%)	
BMI (kg/m^2), median (IQR)	27.8 (24.5–32.5)	27.7 (24.2–32.2)	0.28
Cardiac arrest before ICU admission	246/1160 (21.2%)	1614/16 840 (9.6%)	< 0.001
APACHE III-j risk of death, mean (SD)	0.584 ± 0.288	0.319 ± 0.296	< 0.001
APACHE III-j: five most common ICU diagnosis codes			
1	211 (18.1%)†	1548 (8.7%)‡	
2	200 (17.2%)§	1499 (8.4%)¶	
3	66 (5.7%)**	1419 (8.0%)††	
4	43 (3.7%)‡‡	900 (5.1%)§§	
5	43 (3.7%)¶¶	630 (3.5%)***	
SOFA score, median (IQR)	9 (7–12)	6 (4–8)	< 0.001
Surgical	310 (26.6%)	8355 (47.0%)	< 0.001
Diabetic ketoacidosis	na	na	na
AKI (Stage 2 or 3)	734 (63.1%)	6536 (36.8%)	< 0.001
Septic shock	235 (20.2%)	1793 (10.1%)	< 0.001
pH, median (IQR)	7.15 (7.09–7.19)	7.26 (7.20–7.28)	< 0.001
$Paco_2$ (mmHg), median (IQR)	38 (32–42)	39 (34–42)	< 0.001
Bicarbonate (lowest) (mmol/L), median (IQR)	12 (9–15)	17 (14–20)	< 0.001
Base excess (mmol/L), median (IQR)	–16.8 (–20.4 to –14.3)	–10.9 (–14.8 to –8.4)	< 0.001
Lactate (mmol/L), median (IQR)	7.4 (3.5–12.0)	3.0 (1.5–6.6)	< 0.001
Potassium (highest) (mmol/L), median (IQR)	5.0 (4.5–5.8)	4.8 (4.4–5.4)	< 0.001
Creatinine (highest) (μmol/L), median (IQR)	196 (131–299)	130 (85–222)	< 0.001
Mechanical ventilation	1005 (86.3%)	12 075/17 518 (68.9%)	< 0.001
ECMO	31/1081 (2.9%)	116/5161 (2.2%)	0.27
RRT	448/1076 (41.6%)	1573/5741 (27.4%)	< 0.001
Inotropes/vasopressor	980 (84.2%)	4383/6000 (73.0%)	< 0.001
Hospital mortality	603 (51.8%)	4130 (23.2%)	< 0.001
ICU mortality	543 (46.7%)	3347/17 743 (18.9%)	< 0.001
RRT initiation	448/1076 (41.6%)	1573/5741 (27.4%)	< 0.001
Hospital length of stay (days), median (IQR)	7.4 (1.9–19.5)	10.0 (5.3–18.8)	< 0.001
ICU length of stay (hours), median (IQR)	2.8 (0.9–7.0)	2.7 (1.3–5.4)	0.94

AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; BICAR-ICU = Sodium Bicarbonate to Treat Severe Acidosis in the Critically Ill: a multiple centre randomised clinical trial; BMI = body mass index; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; na = not applicable; $Paco_2$ = arterial partial pressure of carbon dioxide; RRT = renal replacement therapy; SD = standard deviation; SOFA = Sequential Organ Failure Assessment. * This cohort excludes diabetic ketoacidosis, chronic kidney disease (chronic renal failure in this study), and extrinsic acidosis, so that readers can compare with the table in Jaber et al.[8] † #503: Sepsis with shock (other than urinary). ‡ #1207: Coronary artery bypass grafts. § #102: Cardiac arrest. ¶ #503: Sepsis with shock (other than urinary). ** #101: Cardiogenic shock. †† #102: Cardiac arrest. ‡‡ #901: Renal disorders (4th tie). §§ #1206: Valvular heart surgery. ¶¶ #1401: Gastrointestinal perforation/rupture (not peritonitis; 4th tie). *** #901: Renal disorders.

Figure 2. Change of annual incidence and prevalence of moderate metabolic acidosis



Year	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Incidence (per million per year)	320.1	335.0	360.4	399.4	434.2	438.1	463.0	477.0	476.2	420.3	278.1
Prevalence	12.3%	11.8%	11.9%	12.3%	12.5%	12.7%	12.6%	12.3%	11.7%	10.2%	6.7%

Annual incidence and prevalence of moderate metabolic acidosis were indicated as line graphs.

the external validity of the mortality rate reported in the BICAR-ICU trial.

RRT was used in 34.9% (68/195) and 51.5% (100/194) of patients in the intervention and control groups of BICAR-ICU trial respectively, with an overall value of 43.2%. In comparison, RRT use in the Australian and New Zealand ICU patients was 41.6%, supporting the external validity of renal outcomes of the BICAR-ICU trial. However, the prevalence of severe MA using the BICAR-ICU criteria was quite low in Australian and New Zealand ICUs (1.5%).

The BICAR-ICU trial was designed following observations from five French ICUs by Jung and colleagues.[1] In 2011, they reported that the prevalence of metabolic or mixed severe acidaemia of pH < 7.20 within the first 24 hours of ICU admission was 6%. However, only patients with severe MA without hypercapnia were enrolled in the BICAR-ICU study. The study by Jung et al[1] did not report on the ratio of metabolic and mixed acidosis. However, our study found that 56.2% of Australian and New Zealand patients who had pH < 7.20 also had $Paco_2$ > 45 mmHg, suggesting that the prevalence of isolated metabolic acidosis in the previous study may have been about 2.6% if adjusted for hypercapnia. This value would be > 70% higher than found in our study.

A recent guideline on the diagnosis and treatment of MA recommended that the pH not be used alone to identify such patients.[9] Smith and colleagues[10] suggested that < –4 mmol/L of the initial base excess in ICU is a useful predictor for mortality. In the current study, 8.4% of patients in the Australian and New Zealand ICUs were diagnosed with MA by the moderate MA criteria on their ICU admission day based on pH, a base excess lower than –4 mmol/L, and the lack of hypercapnia. Hospital mortality among such patients was as high as that of septic shock in Australian and New Zealand ICUs,[11] and appeared to be increasing in 2018.

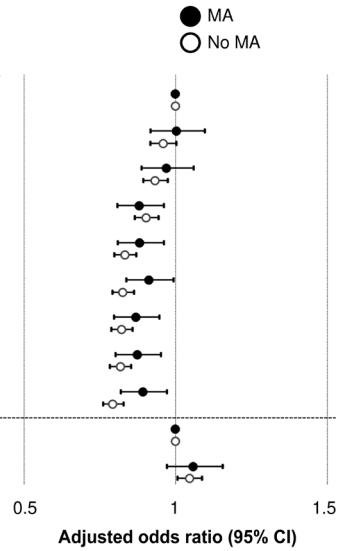
Study implications

In both the BICAR-ICU trial and the current study, patients with severe MA had very high mortality. However, in Australian and New Zealand ICU patients, in the first 24 hours, the prevalence and incidence of the BICAR-ICU trial criteria were low. At about 40 patients per million per year and assuming that, as in previous similar studies, only 30 of 190 ICUs would participate in such a trial and that anticipated recruitment would be 30% of eligible patients as in other trials[12] of acutely ill patients in Australia and New Zealand, this would translate into only about 50 patients randomised per year. As about 550 patients would be required to have a > 80% power to detect a 25% relative risk reduction in mortality from a baseline of 48%, such a trial would require 11 years and would not be feasible in Australia and New Zealand. The same would apply if RRT were the primary outcome.

In contrast, for moderate MA, a 25% decrease in mortality with sodium bicarbonate therapy from 21.5% at

Figure 3. Annual crude hospital mortality of patients with and without moderate metabolic acidosis as well as adjusted annual odds ratio for the hospital mortality

Year of ICU admission	No. of patients		No. of deaths		*P* value for interaction
	MA	No MA	MA	No MA	
2008	8234	58 862	1965 (23.9%)	6349 (10.8%)	
2009	8805	66 079	2092 (23.8%)	6635 (10.0%)	
2010	9635	71 584	2181 (22.6%)	6887 (9.6%)	
2011	10 775	76 942	2247 (20.9%)	7197 (9.4%)	
2012	11 791	82 530	2402 (20.4%)	6861 (8.3%)	0.016
2013	12 104	83 234	2413 (19.9%)	6634 (8.0%)	
2014	12 987	90 170	2334 (18.0%)	7065 (7.8%)	
2015	13 558	96 840	2400 (17.7%)	7316 (7.6%)	
2016	13 755	103 462	2501 (18.2%)	7431 (7.2%)	
2017	12 366	108 918	2523 (20.4%)	7900 (7.3%)	0.78
2018	8313	115 143	1921 (23.1%)	8140 (7.1%)	



ICU = intensive care unit; MA = metabolic acidosis. Numbers of patients and hospital deaths were indicated by with and without moderate metabolic acidosis. The parentheses show the crude mortality rate.

$\alpha = 0.05$ would require the randomisation of 1750 patients to achieve > 80% power. Assuming the observed incidence of 400 per million per year and the same anticipated unit participation and recruitment rate, 540 patients would likely be recruited per year making such a trial feasible in 3 years. If choosing RRT as the outcome, 1250 patients would have to be randomised, making such a trial even more feasible.

Strengths and limitations

The use of a binational database including more a million patients made it possible to provide precise demographics of patients with MA in real-world ICUs. The large sample size enabled us to describe the small population defined by the BICAR-ICU criteria, and to explore subpopulations with or without hypercapnia. The results are widely generalisable to Australian and New Zealand ICUs. They allow reasonably accurate estimates of trial requirements for the design and powering of future randomised controlled trials of an intervention such as sodium bicarbonate.

This study has several limitations. First, its retrospective observational design cannot differentiate whether the observed outcomes were induced by the MA or by other conditions. Second, about one-third of records were excluded mainly due to missing data in diagnostic variables, which might have caused a degree of selection bias. For example, patients who did not have an arterial line might have also had missing data on BGA. Third, the database used in the present study included only laboratory data on the day of ICU admission. Therefore, we could not assess the trends of such variables. Fourth, information on specific treatment such as administration of intravenous sodium bicarbonate was not available.

Conclusions

BICAR-ICU criteria could identify patients with MA carrying high mortality; however, the prevalence of such severe MA was quite low in Australian and New Zealand ICUs, making an interventional trial in such patients non-feasible. Nevertheless, defining MA with broader criteria could identify patients who were still at high risk of death and had a much higher incidence, making a trial in such patients feasible over a period of 3 years in Australia and New Zealand alone. These observations have important implications for the design and powering of a future randomised controlled trial of sodium bicarbonate in these patients.

Competing interests

None declared.

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