Appendix 1. This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Early Metabolic Acidosis in Critically Ill Patients: A Binational Multicentre Study

Methods

2017-2018 period and changes in data collection

The Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD) provided two types of blood gas analysis (BGA) data during the study period, data for Acute Physiology and Chronic Health Evaluation (APACHE) II score calculation and the data for APACHE III-j calculation. We used the latter BGA data for the present study, because base excess (BE) calculation needed pH and $PaCO_2$ values that came from the same blood sample. However, the collection methodology for BGA data in the ANZICS APD was changed in 2016. From 2008 to 2016, the BGA data were selected to deliver the values producing the highest score for the acid-base disturbance component of the APACHE III-j score. In contrast, for 2017 and 2018, the BGA data were instead selected to deliver (e.g. through oxygen tension) the values producing the highest score for the total APACHE III-j score.

Sequential Organ Failure Assessment (SOFA) score

For SOFA score calculation, only available data contributed. In respiratory component, the lowest P/F ratio during the first 24 hours of intensive care unit (ICU) admission were used, and use of mechanical ventilation were considered as need of respiratory support. In cardiovascular component, the lowest mean arterial blood pressure (MAP) during the first 24 hours of ICU admission was used. Patients with MAP < 60 mmHg and use of inotropes/vasopressor, and MAP < 50 mmHg and use of inotropes/vasopressor were assigned 2 point and 4 point, respectively.

The ANZICS APD records the highest and lowest values in platelet count, MAP, and creatinine, highest value of bilirubin, and lowest or at just prior to sedation in the Glasgow Coma Score during the first

24 hours of ICU admission. To calculate the SOFA score, the lowest values of platelet count and MAP, as well as the highest value of creatinine were used.

Diagnostic criteria for metabolic acidosis

- Criteria set # 1: BICAR-ICU criteria (Early Severe metabolic acidosis criteria)

This diagnostic criteria were applied to patients with complete data for the following variables: pH, $PaCO_2$, HCO_3^-, lactate, and use of inotropes/vasopressors, all during the first 24 hours of ICU admission.

- Novel ANZICS Criteria set # 2: Moderate early metabolic acidosis criteria

BE in this diagnostic criteria was calculated using the following formula:

$BE = [0.0307 \times PaCO_2 \times 10^{(pH - 6.105)}] - 24.8 + [16.2 \times (pH - 7.40)]$.[1]

Incidence and prevalence

Incidence was defined as the number of patients with metabolic acidosis diagnosed by each set of criteria per ANZ population for each year. The ANZ population of the year was calculated as the average of published numbers of population on the website at 4 points during the year (March, June, September, December).[2, 3]

Prevalence was defined as a percentage of patients with metabolic acidosis diagnosed by each set of criteria per number of patients evaluated.

Outcome measures

Renal replacement therapy (RRT) initiation in the ICU was defined as RRT provided to patients who did not have dialysis-depend end-stage renal failure at ICU admission.

Definition of subgroups

Subgroups of patients in the tables were defined as following:

- Diabetic ketoacidosis; patients coded with diabetic ketoacidosis in APACHE III-j Diagnosis at ICU admission.
- Post-cardiac arrest (cardiac arrest prior to ICU admission); patients who had a cardiac arrest in the 24 hours prior to ICU admission.
- Chronic renal failure; patients who were coded with chronic renal failure in chronic comorbidities for APACHE II scoring at ICU admission.
- Acute kidney injury of Stage 2 or 3 in the Acute Kidney Injury Network categories; highest creatinine ≥ 200 µmol/L or urine output < 0.5 mL/kg/hour over the first 24 hours of ICU admission. Patients who had chronic renal failure at ICU admission were excluded.
- Septic shock; Coded in APACHE III-j Diagnosis at ICU admission.

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Hospital (Richmond) ICU, Fairfield Hospital ICU, Figtree Private Hospital ICU, Fiona Stanley Hospital ICU, Flinders Medical Centre ICU, Flinders Private Hospital ICU, Footscray Hospital ICU, Frankston Hospital ICU, Fremantle Hospital ICU, Gold Coast Private Hospital ICU, Gold Coast University Hospital ICU, Gosford Hospital ICU, Gosford Private Hospital ICU, Goulburn Base Hospital ICU, Goulburn Valley Health ICU, Grafton Base Hospital ICU, Greenslopes Private Hospital ICU, Griffith Base Hospital ICU, Hawkes Bay Hospital ICU, Hervey Bay Hospital ICU, Hollywood Private Hospital ICU, Holmesglen Private Hospital ICU, Holy Spirit Northside Hospital ICU, Hornsby Ku-ring-gai Hospital ICU, Hurstville Private Hospital ICU, Hutt Hospital ICU, Ipswich Hospital ICU, John Fawkner Hospital ICU, John Flynn Private Hospital ICU, John Hunter Hospital ICU, Joondalup Health Campus ICU, Kareena Private Hospital ICU, Knox Private Hospital ICU, Latrobe Regional Hospital ICU, Launceston General Hospital ICU, Lingard Private Hospital ICU, Lismore Base Hospital ICU, Liverpool Hospital ICU, Logan Hospital ICU, Lyell McEwin Hospital ICU, Mackay Base Hospital ICU, Macquarie University Private Hospital ICU, Manly Hospital & Community Health ICU, Manning Rural Referral Hospital ICU, Maroondah Hospital ICU, Mater Adults Hospital (Brisbane) ICU, Mater Health Services North Queensland ICU, Mater Private Hospital (Brisbane) ICU, Mater Private Hospital (Sydney) ICU, Melbourne Private Hospital ICU, Middlemore Hospital ICU, Mildura Base Hospital ICU, Modbury Public Hospital ICU, Monash Medical Centre-Clayton Campus ICU, Mount Hospital ICU, Mount Isa Hospital ICU, Nambour General Hospital ICU, National Capital Private Hospital ICU, Nelson Hospital ICU, Nepean Hospital ICU, Newcastle Private Hospital ICU, Noosa Hospital ICU, North Shore Hospital ICU, North Shore Private Hospital ICU, North West Regional Hospital (Burnie) ICU, Northeast Health Wangaratta ICU, Norwest Private Hospital ICU, Orange Base Hospital ICU, Peninsula Private Hospital ICU, Peter MacCallum Cancer Institute ICU, Pindara Private Hospital ICU, Port Macquarie Base Hospital ICU, Prince of Wales Hospital (Sydney) ICU, Prince of Wales Private Hospital (Sydney) ICU, Princess Alexandra Hospital ICU, Queen Elizabeth II Jubilee Hospital ICU, Redcliffe Hospital ICU, Repatriation General Hospital (Adelaide) ICU, Robina Hospital ICU, Rockhampton Hospital ICU, Rockingham General Hospital ICU, Rotorua Hospital ICU, Royal Adelaide Hospital ICU, Royal Brisbane and Women's Hospital ICU, Royal Darwin Hospital ICU, Royal Hobart

Hospital ICU, Royal Melbourne Hospital ICU, Royal North Shore Hospital ICU, Royal Perth Hospital ICU, Royal Prince Alfred Hospital ICU, Shoalhaven Hospital ICU, Sir Charles Gairdner Hospital ICU, South West Healthcare (Warrnambool) ICU, Southern Cross Hospital (Hamilton) ICU, Southern Cross Hospital (Wellington) ICU, St Andrew's Hospital (Adelaide) ICU, St Andrew's Hospital Toowoomba ICU, St Andrew's War Memorial Hospital ICU, St George Hospital (Sydney) CICU, St George Hospital (Sydney) ICU, St George Hospital (Sydney) ICU2, St George Private Hospital (Sydney) ICU, St John of God (Berwick) ICU, St John Of God Health Care (Subiaco) ICU, St John Of God Hospital (Ballarat) ICU, St John of God Hospital (Bendigo) ICU, St John Of God Hospital (Geelong) ICU, St John Of God Hospital (Murdoch) ICU, St John of God Midland Public & Private ICU, St Vincent's Hospital (Melbourne) ICU, St Vincent's Hospital (Sydney) ICU, St Vincent's Hospital (Toowoomba) ICU, St Vincent's Private Hospital (Sydney) ICU, St Vincent's Private Hospital Fitzroy ICU, Sunnybank Hospital ICU, Sunshine Coast University Hospital ICU, Sunshine Hospital ICU, Sutherland Hospital & Community Health Services ICU, Sydney Adventist Hospital ICU, Sydney Southwest Private Hospital ICU, Tamworth Base Hospital ICU, Taranaki Health ICU, Tauranga Hospital ICU, The Bays Hospital ICU, The Chris O'Brien Lifehouse ICU, The Memorial Hospital (Adelaide) ICU, The Northern Hospital ICU, The Prince Charles Hospital ICU, The Queen Elizabeth (Adelaide) ICU, The Townsville Hospital ICU, The Valley Private Hospital ICU, The Wesley Hospital ICU, Timaru Hospital ICU, Toowoomba Hospital ICU, Tweed Heads District Hospital ICU, University Hospital Geelong ICU, Wagga Wagga Base Hospital & District Health ICU, Waikato Hospital ICU, Warringal Private Hospital ICU, Wellington Hospital ICU, Werribee Mercy Hospital ICU, Western District Health Service (Hamilton) ICU, Western Hospital (SA) ICU, Western Private Hospital ICU, Westmead Hospital ICU, Westmead Private Hospital ICU, Whangarei Area Hospital, Northland Health Ltd ICU, Wimmera Health Care Group (Horsham) ICU, Wollongong Hospital ICU, Wollongong Private Hospital ICU, and Wyong Hospital ICU.

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

	Overall	BICAR-ICU severe acidosis	Moderate metabolic acidosis	*P* value
Number of patients (%)	244,740	1,350 / 87,110* (1.5)	20,679 / 244,740 (8.4)	<0.001
Age, years	62.8 ± 17.0	62.7 ± 16.7	62.1 ± 17.4	0.16
Sex				0.56
Male, n (%)	142,438 (58.2)	732 (54.2)	11,529 (55.8)	
Female, n (%)	102,171 (41.7)	618 (45.8)	9,142 (44.2)	
Other/Unknown, n (%)	131 (0.1)	0 (0)	8 (<0.1)	
Height, cm	170 (162, 177)	170 (161, 175)	170 (162, 176)	0.47
Weight, kg	80.0 (68.0, 95.0)	80.0 (67.2, 92.6)	80.0 (67.0, 94.0)	0.89
BMI, kg/m^2	27.7 (24.2, 32.5)	27.7 (24.3, 32.5)	27.6 (24.0, 32.1)	0.26
Chronic health evaluation of APACHE II				
Respiratory, n (%)	17,033 / 244,717 (7.0)	71 (5.3)	1,057 (5.1)	0.86
Cardiovascular, n (%)	19,061 / 244,717 (7.8)	96 (7.1)	1,552 (7.5)	0.63
Liver, n (%)	4,220 / 244,717 (1.7)	60 (4.4)	543 (2.6)	<0.001
Renal, n (%)	7,740 / 244,717 (3.2)	85 (6.3)	1,109 (5.4)	0.16
Immune Suppressive Disease, n (%)	7,250 / 244,717 (3.0)	38 (2.8)	472 (2.3)	0.24
Immunosuppressive therapy, n (%)	12,135 / 244,717 (5.0)	86 (6.4)	1,095 (5.3)	0.10
Planned admission, n (%)	118,496 / 242,269 (48.9)	217 (16.1)	6,098 / 20,429 (29.8)	<0.001
Treatment limitation order at ICU admission, n (%)	14,021 / 242,301 (5.8)	205 (15.2)	1,670 / 20,400 (8.2)	<0.001
Cardiac arrest prior to ICU admission, n (%)	7,442 / 236,109 (3.2)	259 / 1,344 (19.3)	1,708 / 19,540 (8.7)	<0.001
APACHE III-j score	50 (38, 66)	103 (81, 127)	73 (54, 96)	<0.001
APACHE III-j risk of death	0.141 ± 0.199	0.544 ± 0.307	0.298 ± 0.293	<0.001
Risk of death by ANZROD	0.089 ± 0.167	0.447 ± 0.317	0.211 ± 0.266	<0.001
SOFA score, Total	4 (2, 6)	9 (6, 12)	6 (3, 8)	<0.001
Respiratory	2 (1, 2)	2 (1, 3)	2 (1, 3)	<0.001
Haematological	0 (0, 1)	0 (0, 2)	0 (0, 1)	<0.001
Hepatic	0 (0, 0)	0 (0, 2)	0 (0, 1)	<0.001
Cardiovascular	1 (0, 1)	1 (1, 2)	1 (0, 1)	<0.001
Neurologic	0 (0, 1)	1 (0, 3)	0 (0, 1)	<0.001
Renal	0 (0, 1)	3 (1, 4)	1 (0, 3)	<0.001
Diagnostic categories in APACHE III-j				<0.001
Cardiovascular, n (%)	66,686 (27.2)	413 (30.6)	6,578 (31.8)	
Respiratory, n (%)	34,119 (13.9)	60 (4.4)	1,517 (7.3)	
Gastrointestinal, n (%)	40,713 (16.6)	241 (17.9)	3,512 (17.0)	
Neurological, n (%)	29,625 (12.1)	22 (1.6)	909 (4.4)	
Sepsis, n (%)	19,302 (7.9)	308 (22.8)	2,742 (13.3)	
Trauma, n (%)	10,652 (4.4)	43 (3.2)	992 (4.8)	
Metabolic, n (%)	15,033 (6.1)	139 (10.3)	2,306 (11.2)	
Haematological, n (%)	942 (0.4)	9 (0.7)	75 (0.4)	
Renal/Genitourinary, n (%)	8,985 (3.7)	71 (5.3)	1,249 (6.0)	
Gynaecological, n (%)	3,109 (1.3)	9 (0.7)	186 (0.9)	
Musculoskeletal/Skin disease, n (%)	14,548 (5.9)	27 (2.0)	529 (2.6)	
Undefined n (%)	1,026 (0.4)	8 (0.6)	84 (0.4)	
Five most common ICU diagnostic				

codes of APACHE III-j				
1, n (%)	#1207: Coronary artery bypass grafts, 19,723 (8.1)	#503: Sepsis with shock (other than urinary), 222 (16.4)	#1207: Coronary artery bypass grafts, 1,597 (7.7)	
2, n (%)	#1405: Gastrointestinal neoplasm, 11,662 (4.8)	#102: Cardiac arrest, 208 (15.4)	#503: Sepsis with shock (other than urinary), 1,575 (7.6)	
3, n (%)	#1206: Valvular heart surgery, 11,525 (4.7)	#702: Diabetic ketoacidosis, 74 (5.5)	#102: Cardiac arrest, 1,484 (7.2)	
4, n (%)	#1902: Orthopaedic surgery, 11,267 (4.6)	#101: Cardiogenic shock, 69 (5.1)	#702: Diabetic ketoacidosis, 1,124 (5.4)	
5, n (%)	#1408: Other Gastrointestinal diseases, 9,238 (3.8)	#901: Renal disorders, 53 (3.9)	#1206: Valvular heart surgery, 917 (4.4)	
Medical, n (%)	100,465 (41.0)	1,016 (75.3)	11,908 (57.6)	<0.001
Surgical, n (%)	144,275 (59.0)	334 (24.7)	8,771 (42.4)	<0.001
Diabetic ketoacidosis, n (%)	2,665 (1.1)	74 (5.5)	1,124 (5.4)	0.99
AKI (Stage 2 or 3), n (%)	38,562 (15.8)	759 (56.2)	6,819 (33.0)	<0.001
Septic shock, n (%)	10,531 (4.3)	247 (18.3)	1,886 (9.1)	<0.001
pH	7.37 (7.31, 7.41)	7.15 (7.08, 7.18)	7.26 (7.19, 7.28)	<0.001
$PaCO_2$, mmHg	40 (35, 46)	37 (31, 42)	39 (33, 42)	<0.001
$PaCO_2$ > 45mmHg, n (%)	61,967 (25.3)	N/A	N/A	N/A
Bicarbonate (highest), mmol/L	24 (22, 26)	17 (14, 20)	20 (17, 23)	<0.001
Bicarbonate (lowest), mmol/L	22 (20, 24)	12 (9, 15)	17 (13, 20)	<0.001
Base excess, mmol/L	-2.4 (-5.4, 0.2)	-17.2 (-21.0, -14.4)	-11.2 (-15.3, -8.5)	<0.001
Lactate, mmol/L	1.6 (1.0, 2.5)	7.0 (3.0, 11.8)	2.9 (1.4, 6.1)	<0.001
Lactate > 2mmol/L, n (%)	38,171 / 113,389 (33.7)	1,111 (82.3)	4,068 / 6,716 (60.6)	<0.001
Potassium (highest), mmol/L	4.4 (4.1, 4.8)	5.0 (4.5, 5.8)	4.8 (4.3, 5.4)	<0.001
Potassium (lowest), mmol/L	4.0 (3.6, 4.3)	3.9 (3.5, 4.5)	4.0 (3.6, 4.5)	0.002
Creatinine (highest), µmol/L	84 (65, 119)	198 (132, 311)	132 (85, 235)	<0.001
Creatinine (lowest), µmol/L	75 (59, 103)	153 (100, 244)	106 (71, 186)	<0.001
Urine output during the first 24 hours in the ICU, mL	1,565 (1,057, 2,260)	743 (177, 1,730)	1,386 (730, 2,200)	<0.001
Treatments in the ICU				
Mechanical ventilation, n (%)	111,837 / 241,186 (46.4)	1,115 (82.6)	13,305 / 20,418 (65.2)	<0.001
Time on invasive ventilation, hours	17 (8, 58)	48 (17, 130)	37 (13, 109)	<0.001
ECMO, n (%)	479 / 99,675 (0.5)	32 / 1,260 (2.5)	118 / 6,027 (2.0)	0.23
RRT, n (%)	6,119 / 101,483 (6.0)	519 / 1,251 (41.5)	1,857 / 6,758 (27.5)	<0.001
Inotropes/vasopressor, n (%)	45,727 / 105,450 (43.4)	1,098 (81.3)	4,873 / 7,074 (68.9)	<0.001
Outcomes				
Hospital mortality, n (%)	20,484 (8.4)	652 (48.3)	4,444 (21.5)	<0.001
ICU mortality, n (%)	13,584 / 244,263 (5.6)	587 / 1,348 (43.5)	3,583 / 20,653 (17.3)	<0.001
RRT initiation, n (%)	4,888 / 97,669 (5.0)	468 / 1,170 (40.0)	1,637 / 6,287 (26.0)	<0.001
Hospital length of stay, days	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	1.8 (0.9, 3.6)	2.8 (1.0, 6.8)	2.6 (1.2, 5.1)	0.28

Data as n (%), means ± standard deviation, or median (interquartile range).AKI: acute kidney injury; ANZROD: Australian and New Zealand risk of death[4]; APACHE: acute physiology and chronic health evaluation; BMI: body mass index; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; RRT: renal replacement therapy; SOFA: sequential organ failure assessment.*157,630 patients excluded due to missing data

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* value
Number of patients, n (%)	1,164 / 80,610 (1.4%)	17,764 / 226,832 (7.8%)	<0.001
Age, years	64.2 ± 16.0	63.9 ± 16.3	0.50
Sex			0.65
Male, n (%)	643 (55.2)	10,029 (56.5)	
Female, n (%)	521 (44.8)	7,727 (43.5)	
Other/Unknown, n (%)	0 (0)	8 (<0.1)	
Height, cm	170 (162, 175)	170 (162, 176)	0.82
Weight, kg	80.0 (69.4, 93.0)	80.0 (68.0, 95.0)	0.88
BMI, kg/m^2	27.8 (24.5, 32.5)	27.7 (24.2, 32.2)	0.28
Chronic health evaluation in APACHE II			
Respiratory, n (%)	57 (4.9)	916 (5.2)	0.75
Cardiovascular, n (%)	77 (6.6)	1,276 (7.2)	0.50
Liver, n (%)	51 (4.4)	492 (2.8)	0.002
Renal, n (%)	N/A	N/A	N/A
Immune Suppressive Disease, n (%)	34 (2.9)	435 (2.4)	0.37
Immunosuppressive therapy, n (%)	77 (6.6)	958 (5.4)	0.09
Planned ICU admission, n (%)	201 (17.3)	5,763 / 17,564 (32.8)	<0.001
Treatment limitation order at ICU admission, n (%)	186 (16.0)	1,482 / 17,519 (8.5)	<0.001
Cardiac arrest prior to ICU admission, n (%)	246 / 1,160 (21.2)	1,614 / 16,840 (9.6)	<0.001
APACHE III-j score	105 (85, 128)	73 (55, 98)	<0.001
APACHE III-j risk of death	0.584 ± 0.288	0.319 ± 0.296	<0.001
Risk of death by ANZROD	0.481 ± 0.307	0.228 ± 0.271	<0.001
SOFA score	9 (7, 12)	6 (4, 8)	<0.001
Respiratory	2 (1, 3)	2 (1, 3)	<0.001
Haematological	0 (0, 2)	0 (0, 1)	<0.001
Hepatic	0 (0, 2)	0 (0, 1)	<0.001
Cardiovascular	1 (1, 2)	1 (1, 1)	<0.001
Neurologic	1 (0, 3)	0 (0, 1)	<0.001
Renal	3 (1, 4)	1 (0, 3)	<0.001
Diagnostic category in APACHE III-j			<0.001
Cardiovascular, n (%)	392 (33.7)	6,305 (35.5)	
Respiratory, n (%)	60 (5.2)	1,441 (8.1)	
Gastrointestinal, n (%)	229 (19.7)	3,357 (18.9)	
Neurological, n (%)	19 (1.6)	868 (4.9)	
Sepsis, n (%)	290 (24.9)	2,553 (14.4)	
Trauma, n (%)	43 (3.7)	974 (5.5)	
Metabolic, n (%)	26 (2.2)	401 (2.3)	
Haematological, n (%)	9 (0.8)	74 (0.4)	
Renal/Genitourinary, n (%)	56 (4.8)	1,034 (5.8)	
Gynaecological, n (%)	9 (0.8)	183 (1.0)	
Musculoskeletal/Skin disease, n (%)	24 (2.1)	494 (2.8)	
Undefined/Unknown, n (%)	7 (0.6)	80 (0.5)	
Five most common ICU diagnosis codes of APACHE III-j			
1, n (%)	#503: Sepsis with shock (other than urinary), 211 (18.1)	#1207: Coronary artery bypass grafts, 1,548 (8.7)	
2, n (%)	#102: Cardiac arrest, 200 (17.2)	#503: Sepsis with shock (other	

		than urinary), 1,499 (8.4)	
3, n (%)	#101: Cardiogenic shock, 66 (5.7)	#102: Cardiac arrest, 1,419 (8.0)	
4, n (%)	#901: Renal disorders, 43 (3.7) (4th tie)	#1206: Valvular heart surgery, 900 (5.1)	
5, n (%)	#1401: Gastrointestinal perforation/rupture (not peritonitis), 43 (3.7) (4th tie)	#901: Renal disorders, 630 (3.5)	
Medical, n (%)	854 (73.4)	9,409 (53.0)	<0.001
Surgical, n (%)	310 (26.6)	8,355 (47.0)	<0.001
Diabetic ketoacidosis, n (%)	N/A	N/A	N/A
AKI (Stage 2 or 3), n (%)	734 (63.1)	6,536 (36.8)	<0.001
Septic shock, n (%)	235 (20.2)	1,793 (10.1)	<0.001
pH	7.15 (7.09, 7.19)	7.26 (7.20, 7.28)	<0.001
$PaCO_2$, mmHg	38 (32, 42)	39 (34, 42)	<0.001
$PaCO_2$ > 45mmHg, n (%)	N/A	N/A	N/A
Bicarbonate (highest), mmol/L	17 (14, 20)	21 (18, 23)	<0.001
Bicarbonate (lowest), mmol/L	12 (9, 15)	17 (14, 20)	<0.001
Base excess, mmol/L	-16.8 (-20.4, -14.3)	-10.9 (-14.8, -8.4)	<0.001
Lactate, mmol/L	7.4 (3.5, 12.0)	3.0 (1.5, 6.6)	<0.001
Lactate > 2mmol/L, n (%)	981 (84.3)	3,596 / 5,726 (62.8)	<0.001
Potassium (highest), mmol/L	5.0 (4.5, 5.8)	4.8 (4.4, 5.4)	<0.001
Potassium (lowest), mmol/L	3.9 (3.5, 4.5)	4.0 (3.6, 4.5)	0.006
Creatinine (highest), µmol/L	196 (131, 299)	130 (85, 222)	<0.001
Creatinine (lowest), µmol/L	151 (100, 234)	105 (72, 175)	<0.001
Urine output for first 24 hours, mL	704 (167, 1,550)	1,340 (725, 2,070)	<0.001
Mechanical ventilation, n (%)	1,005 (86.3)	12,075 / 17,518 (68.9)	<0.001
Length of invasive ventilation, hours	49 (17, 133)	39 (13, 114)	0.001
ECMO, n (%)	31 / 1,081 (2.9)	116 / 5,161 (2.2)	0.27
RRT, n (%)	448 / 1,076 (41.6)	1,573 / 5,741 (27.4)	<0.001
Inotropes/vasopressor, n (%)	980 (84.2)	4,383 / 6,000 (73.0)	<0.001
Outcomes			
Hospital mortality, n (%)	603 (51.8)	4,130 (23.2)	<0.001
ICU mortality, n (%)	543 (46.7)	3,347 / 17,743 (18.9)	<0.001
RRT initiation, n (%)	448 / 1,076 (41.6)	1,573 / 5,741 (27.4)	<0.001
Hospital length of stay, days	7.4 (1.9, 19.5)	10.0 (5.3, 18.8)	<0.001
ICU length of stay, hours	2.8 (0.9, 7.0)	2.7 (1.3, 5.4)	0.94

*This cohort excludes diabetic ketoacidosis, chronic kidney disease (chronic renal failure in this study), and extrinsic acidosis, so that readers can compare to the table of BICAR-ICU paper in the Lancet.
Data are presented as n (%), means ± standard deviation, or median (interquartile range).
AKI: acute kidney injury; ANZROD: Australian and New Zealand risk of death; APACHE: acute physiology and chronic health evaluation; BMI: body mass index; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; RRT: renal replacement therapy; SOFA: sequential organ failure assessment.

Table S1. Patient characteristics and outcomes of patients with and without metabolic acidosis diagnosed with the BICAR-ICU criteria

	Without BICAR-ICU severe acidosis	With BICAR-ICU severe acidosis	*P* value
Number of patients (%)	85,760 / 87,1110 (98.5)	1,350 / 87,110 (1.5)	
Age, years	62.9 ± 17.0	62.7 ± 16.7	0.69
Sex			0.003
Male, n (%)	50,404 (58.8)	732 (54.2)	
Female, n (%)	35,282 (45.9)	618 (45.8)	
Other/Unknown, n (%)	74 (0.1)	0 (0)	
Height, cm	170 (162, 177)	170 (161, 175)	0.04
Weight, kg	80.0 (68.0, 95.0)	80.0 (67.2, 92.6)	0.22
BMI, kg/m^2	27.7 (24.1, 32.5)	27.7 (24.3, 32.5)	0.78
Chronic health evaluation of APACHE II			
Respiratory, n (%)	6,678 / 85,737 (7.8)	71 (5.3)	0.001
Cardiovascular, n (%)	7,507 / 85,737 (8.8)	96 (7.1)	0.04
Liver, n (%)	1,453 / 85,737 (1.7)	60 (4.4)	<0.001
Renal, n (%)	2,916 / 85,737 (3.4)	85 (6.3)	<0.001
Immune Suppressive Disease, n (%)	3,582 / 85,737 (4.2)	38 (2.8)	0.02
Immunosuppressive therapy, n (%)	4,915 / 85,737 (5.7)	86 (6.4)	0.35
Planned ICU admission, n (%)	43,078 / 85,753 (50.2)	217 (16.1)	<0.001
Treatment limitation order at ICU admission, n (%)	5,557 / 85,658 (6.5)	205 (15.2)	<0.001
Cardiac arrest prior to ICU admission, n (%)	2,767 / 85,372 (3.2)	259 / 1,344 (19.3)	<0.001
APACHE III-j score	50 (38, 66)	103 (81, 127)	<0.001
APACHE III-j risk of death	0.137 ± 0.190	0.544 ± 0.307	<0.001
Risk of death by ANZROD	0.089 ± 0.163	0.447 ± 0.317	<0.001
SOFA score, Total	4 (2, 6)	9 (6, 12)	<0.001
Respiratory	2 (1, 2)	2 (1, 3)	<0.001
Haematological	0 (0, 1)	0 (0, 2)	<0.001
Hepatic	0 (0, 0)	0 (0, 2)	<0.001
Cardiovascular	1 (0, 1)	1 (1, 2)	<0.001
Neurologic	0 (0, 1)	1 (0, 3)	<0.001
Renal	0 (0, 1)	3 (1, 4)	<0.001
Diagnostic categories in APACHE III-j			<0.001
Cardiovascular, n (%)	24,131 (28.1)	413 (30.6)	
Respiratory, n (%)	11,698 (13.6)	60 (4.4)	
Gastrointestinal, n (%)	14,308 (16.7)	241 (17.9)	
Neurological, n (%)	9,951 (11.6)	22 (1.6)	
Sepsis, n (%)	7,105 (8.3)	308 (22.8)	
Trauma, n (%)	4,396 (5.1)	43 (3.2)	
Metabolic, n (%)	5,099 (5.9)	139 (10.3)	
Haematological, n (%)	343 (0.4)	9 (0.7)	
Renal/Genitourinary, n (%)	2,855 (3.3)	71 (5.3)	
Gynaecological, n (%)	992 (1.2)	9 (0.7)	
Musculoskeletal/Skin disease, n (%)	4,718 (5.5)	27 (2.0)	
Undefined/Unknown, n (%)	164 (0.2)	8 (0.6)	
Five most common ICU diagnosis codes of APACHE III-j			
1, n (%)	#1207: Coronary artery bypass grafts, 7,220 (8.4)	#503: Sepsis with shock (other than urinary), 222 (16.4)	
2, n (%)	#1405: Gastrointestinal	#102: Cardiac arrest, 208 (15.4)	

	neoplasm, 4,329 (5.0)		
3, n (%)	#1206: Valvular heart surgery, 4,117 (4.8)	#702: Diabetic ketoacidosis, 74 (5.5)	
4, n (%)	#1902: Orthopaedic surgery, 3,634 (4.2)	#101: Cardiogenic shock, 69 (5.1)	
5, n (%)	#1408: Other gastrointestinal diseases, 3,146 (3.7)	#901: Renal disorders, 53 (3.9)	
Medical, n (%)	35,136 (41.0)	1,016 (75.3)	<0.001
Surgical, n (%)	50,624 (59.0)	334 (24.7)	<0.001
Diabetic ketoacidosis, n (%)	839 (1.0)	74 (5.5)	<0.001
AKI (Stage 2 or 3), n (%)	15,196 (17.7)	759 (56.2)	<0.001
Septic shock, n (%)	3,912 (4.6)	247 (18.3)	<0.001
pH	7.38 (7.33, 7.42)	7.15 (7.08, 7.18)	<0.001
$PaCO_2$, mmHg	40 (35, 45)	37 (31, 42)	<0.001
$PaCO_2$ > 45mmHg, n (%)	20,926 (24.4)	N/A	N/A
Bicarbonate (highest), mmol/L	24 (22, 26)	17 (14, 20)	<0.001
Bicarbonate (lowest), mmol/L	22 (20, 24)	12 (9, 15)	
Base excess, mmol/L	-2.2 (-4.8, 0.3)	-17.2 (-21.0, -14.4)	<0.001
Lactate, mmol/L	1.7 (1.0, 2.6)	7.0 (3.0, 11.8)	<0.001
Lactate > 2mmol/L, n (%)	29,615 (34.5)	1,111 (82.3)	<0.001
Potassium (highest), mmol/L	4.4 (4.1, 4.8)	5.0 (4.5, 5.8)	<0.001
Potassium (lowest), mmol/L	3.9 (3.6, 4.3)	3.9 (3.5, 4.5)	0.08
Creatinine (highest), µmol/L	83 (65, 118)	198 (132, 311)	<0.001
Creatinine (lowest), µmol/L	75 (60, 103)	153 (100, 244)	<0.001
Urine output during the first 24 hours in the ICU, mL	1,570 (1,075, 2,260)	743 (177, 1,730)	<0.001
Treatments in the ICU			
Mechanical ventilation, n (%)	45,002 / 85,752 (52.5)	1,115 (82.6)	<0.001
Length of invasive ventilation, hours	18 (8, 60)	48 (17, 130)	<0.001
ECMO, n (%)	290 / 82,687 (0.4)	32 / 1,260 (2.5)	<0.001
RRT, n (%)	3,628 / 81,812 (4.4)	519 / 1,251 (41.5)	<0.001
Inotropes/vasopressor, n (%)	37,869 (44.2)	1,098 (81.3)	<0.001
Outcomes			
Hospital mortality, n (%)	7,086 (8.3)	652 (48.3)	<0.001
ICU mortality, n (%)	4,549 / 85,575 (5.3)	587 / 1,348 (43.5)	<0.001
RRT initiation, n (%)	2,832 / 78,992 (3.6)	468 / 1,170 (40.0)	<0.001
Hospital length of stay, days	9.0 (5.2, 16.0)	7.6 (2.1, 18.9)	<0.001
ICU length of stay, days	1.9 (1.0, 3.7)	2.8 (1.0, 6.8)	<0.001

Data are presented as n (%), means ± standard deviation, or median (interquartile range).
AKI: acute kidney injury; ANZROD: Australian and New Zealand risk of death; APACHE: acute physiology and chronic health evaluation; BMI: body mass index; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; RRT: renal replacement therapy; SOFA: sequential organ failure assessment.

Table S2. Characteristics and outcomes of patients with and without metabolic acidosis diagnosed with the moderate metabolic acidosis criteria

	Without moderate metabolic acidosis	With moderate metabolic acidosis	*P* value
Number of patients (%)	224,061 / 244,740 (91.6)	20,679 / 244,740 (8.4)	
Age, years	62.9 ± 17.0	62.1 ± 17.4	<0.001
Sex			<0.001
Male, n (%)	130,909 (58.4)	11,529 (55.8)	
Female, n (%)	93,029 (41.5)	9,142 (44.2)	
Other/Unknown, n (%)	123 (0.1)	8 (<0.1)	
Height, cm	170 (162, 177)	170 (162, 176)	<0.001
Weight, kg	80.0 (68.0, 95.0)	80.0 (67.0, 94.0)	<0.001
BMI, kg/m^2	27.8 (24.2, 32.6)	27.6 (24.0, 32.1)	<0.001
Chronic health evaluation of APACHE II			
Respiratory, n (%)	15,976 / 224,038 (7.1)	1,057 (5.1)	<0.001
Cardiovascular, n (%)	17,509 / 224,038 (7.8)	1,552 (7.5)	0.12
Liver, n (%)	3,677 / 224,038 (1.6)	543 (2.6)	<0.001
Renal, n (%)	6,631 / 224,038 (3.0)	1,109 (5.4)	<0.001
Immune Suppressive Disease, n (%)	6,778 / 224,038 (3.0)	472 (2.3)	<0.001
Immunosuppressive therapy, n (%)	11,040 / 224,038 (4.9)	1,095 (5.3)	0.02
Planned ICU admission, n (%)	112,398 / 221,840 (50.7)	6,098 / 20,429 (29.8)	<0.001
Treatment limitation order at ICU admission, n (%)	12,351 / 221,901 (5.6)	1,670 / 20,400 (8.2)	<0.001
Cardiac arrest prior to ICU admission, n (%)	5,734 / 216,569 (2.6)	1,708 / 19,540 (8.7)	<0.001
APACHE III-j score	49 (37, 64)	73 (54, 96)	<0.001
APACHE III-j risk of death	0.126 ± 0.181	0.298 ± 0.293	<0.001
Risk of death by ANZROD	0.078 ± 0.150	0.211 ± 0.266	<0.001
SOFA score, Total	3 (2, 5)	6 (3, 8)	<0.001
Respiratory	2 (1, 2)	2 (1, 3)	<0.001
Haematological	0 (0, 1)	0 (0, 1)	<0.001
Hepatic	0 (0, 0)	0 (0, 1)	<0.001
Cardiovascular	1 (0, 1)	1 (0, 1)	<0.001
Neurologic	0 (0, 1)	0 (0, 1)	<0.001
Renal	0 (0, 1)	1 (0, 3)	<0.001
Diagnostic categories in APACHE III-j			<0.001
Cardiovascular, n (%)	60,108 (26.8)	6,578 (31.8)	
Respiratory, n (%)	32,602 (14.6)	1,517 (7.3)	
Gastrointestinal, n (%)	37,201 (16.6)	3,512 (17.0)	
Neurological, n (%)	28,716 (12.8)	909 (4.4)	
Sepsis, n (%)	16,560 (7.4)	2,742 (13.3)	
Trauma, n (%)	9,660 (4.3)	992 (4.8)	
Metabolic, n (%)	12,727 (5.7)	2,306 (11.2)	
Haematological, n (%)	867 (0.4)	75 (0.4)	
Renal/Genitourinary, n (%)	7,736 (3.5)	1,249 (6.0)	
Gynaecological, n (%)	2,923 (1.3)	186 (0.9)	
Musculoskeletal/Skin disease, n (%)	14,019 (6.3)	529 (2.6)	
Undefined/Unknown, n (%)	942 (0.4)	84 (0.4)	
Five most common ICU diagnosis codes of APACHE III-j			
1, n (%)	#1207: Coronary artery bypass grafts, 18,126 (8.1)	#1207: Coronary artery bypass grafts, 1,597 (7.7)	
2, n (%)	#1405: Gastrointestinal	#503: Sepsis with shock (other	

	neoplasm, 11,030 (4.9)	than urinary), 1,575 (7.6)	
3, n (%)	#1902: Orthopaedic surgery, 10,976 (4.9)	#102: Cardiac arrest, 1,484 (7.2)	
4, n (%)	#1206: Valvular heart surgery, 10,608 (4.7)	#702: Diabetic ketoacidosis, 1,124 (5.4)	
5, n (%)	#1504: Laminectomy/Spinal cord surgery, 8,776 (3.9)	#1206: Valvular heart surgery, 917 (4.4)	
Medical, n (%)	88,557 (39.5)	11,908 (57.6)	<0.001
Surgical, n (%)	135,504 (60.5)	8,771 (42.4)	<0.001
Diabetic ketoacidosis, n (%)	1,541 (0.7)	1,124 (5.4)	<0.001
AKI (Stage 2 or 3), n (%)	31,743 (14.2)	6,819 (33.0)	<0.001
Septic shock, n (%)	8,645 (3.9)	1,886 (9.1)	<0.001
pH	7.38 (7.33, 7.42)	7.26 (7.19, 7.28)	<0.001
$PaCO_2$, mmHg	40 (36, 46)	39 (33, 42)	<0.001
$PaCO_2$ > 45mmHg, n (%)	61,967 (27.7)	N/A	N/A
Bicarbonate (highest), mmol/L	24 (22, 27)	20 (17, 23)	<0.001
Bicarbonate (lowest), mmol/L	23 (20, 25)	17 (13, 20)	<0.001
Base excess, mmol/L	-2.0 (-4.5, 0.4)	-11.2 (-15.3, -8.5)	<0.001
Lactate, mmol/L	1.6 (1.0, 2.4)	2.9 (1.4, 6.1)	<0.001
Lactate > 2mmol/L, n (%)	34,103 / 106,673 (32.0)	4,068 / 6,716 (60.6)	<0.001
Potassium (highest), mmol/L	4.4 (4.1, 4.8)	4.8 (4.3, 5.4)	<0.001
Potassium (lowest), mmol/L	3.9 (3.6, 4.3)	4.0 (3.6, 4.5)	<0.001
Creatinine (highest), µmol/L	82 (65, 112)	132 (85, 235)	<0.001
Creatinine (lowest), µmol/L	73 (59, 99)	106 (71, 186)	<0.001
Urine output during the first 24 hours in the ICU, mL	1,582 (1,085, 2,270)	1,386 (730, 2,200)	<0.001
Treatments in the ICU			
Mechanical ventilation, n (%)	98,532 / 220,768 (44.6)	13,305 / 20,418 (65.2)	<0.001
Length of invasive ventilation, hours	17 (8, 50)	37 (13, 109)	<0.001
ECMO, n (%)	361 / 93,648 (0.4)	118 / 6,027 (2.0)	<0.001
RRT, n (%)	4,262 / 94,725 (4.5)	1,857 / 6,758 (27.5)	<0.001
Inotropes/vasopressor, n (%)	40,854 / 98,376 (41.5)	4,873 / 7,074 (68.9)	<0.001
Outcomes			
Hospital mortality, n (%)	16,040 (7.2)	4,444 (21.5)	<0.001
ICU mortality, n (%)	10,001 / 223,610 (4.5)	3,583 / 20,653 (17.3)	<0.001
RRT initiation, n (%)	3,251 / 91,382 (3.6)	1,637 / 6,287 (26.0)	<0.001
Hospital length of stay, days	8.7 (5.1, 15.1)	9.3 (4.7, 17.8)	<0.001
ICU length of stay, days	1.8 (0.9, 3.4)	2.6 (1.2, 5.1)	<0.001

Data are presented as n (%), means ± standard deviation, or median (interquartile range).
AKI: acute kidney injury; ANZROD: Australian and New Zealand risk of death; APACHE: acute physiology and chronic health evaluation; BMI: body mass index; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; RRT: renal replacement therapy; SOFA: sequential organ failure assessment.

Table S3. Prevalence and outcomes of patients in each subgroup

	Overall	BICAR-ICU severe acidosis	*P* vale*	Moderate metabolic acidosis	*P* value*	*P* value**
Diabetic ketoacidosis						
Number of patients, n (%)	2,665 / 244,740 (1.1)	74 / 913 (8.1)		1,124 / 2,665 (42.2)		<0.001
Hospital mortality, n (%)	38 / 2,665 (1.4)	2 / 74 (2.7)	0.19	14 / 1,124 (1.2)	0.61	0.26
ICU mortality, n (%)	20 / 2,662 (0.8)	2 / 74 (2.7)	0.10	10 / 1,122 (0.9)	0.63	0.17
RRT initiation, n (%)	30 / 1,046 (2.9)	6 / 65 (9.2)	0.001	16 / 301 (5.3)	0.005	0.25
Post-cardiac arrest						
Number of patients, n (%)	7,442 / 236,109 (3.2)	259 / 3,026 (8.6)		1,708 / 7,442 (23.0)		<0.001
Hospital mortality, n (%)	3,364 / 7,442 (45.2)	182/ 259 (70.3)	<0.001	1,003 / 1,708 (58.7)	<0.001	0.001
ICU mortality, n (%)	2,969 / 7,436 (39.9)	168 / 259 (64.9)	<0.001	917 / 1,707 (53.7)	<0.001	0.001
RRT initiation, n (%)	475 / 3,219 (14.8)	76 / 228 (33.3)	<0.001	171 / 657 (26.0)	<0.001	0.04
Chronic renal failure						
Number of patients, n (%)	7,740 / 244,717 (3.2)	85 / 3,001 (2.8)		1,109 / 7,740 (21.0)		<0.001
Hospital mortality, n (%)	1,194 / 7,740 (15.4)	41 / 85 (48.2)	<0.001	260 / 1,109 (23.4)	<0.001	<0.001
ICU mortality, n (%)	703 / 7,722 (9.1)	36 / 85 (42.4)	<0.001	189 / 1,108 (17.1)	<0.001	<0.001
RRT initiation, n (%)	N/A	N/A	N/A	N/A	N/A	N/A
AKI of stage 2 and 3 in AKIN categories						
Number of patients, n (%)	38,562 / 244,740 (15.8)	759 / 15,955 (4.8)		6,819 / 38,562 (17.7)		<0.001
Hospital mortality, n (%)	6,899 / 38,562 (17.9)	412 / 759 (54.3)	<0.001	2,295 / 6,819 (33.7)	<0.001	<0.001
ICU mortality, n (%)	5,046 / 38,494 (13.1)	370 / 758 (48.8)	<0.001	1,885 / 6,811 (27.7)	<0.001	<0.001
RRT initiation, n (%)	3,619 / 18,525 (19.5)	373 / 711 (52.5)	<0.001	1,298 / 2,779 (46.7)	<0.001	0.007
Septic shock						
Number of patients, n (%)	10,531 / 244,740 (4.3)	247 / 4,159 (5.9)		1,886 / 10,531 (17.9)		<0.001
Hospital mortality, n (%)	2,158 / 10,531 (20.5)	140 / 247 (56.7)	<0.001	706 / 1,886 (37.4)	<0.001	<0.001
ICU mortality, n (%)	1,518 /10,516 (14.4)	129 / 247 (52.2)	<0.001	580 / 1,884 (30.8)	<0.001	<0.001
RRT initiation, n (%)	826 / 4,299 (19.2)	129 / 220 (58.6)	<0.001	342 / 736 (46.5)	<0.001	0.002

Data are presented as n (%).
AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; ICU: intensive care unit; RRT: renal replacement therapy.
*the P value indicates comparison between patients in positive and negative of each criteria.
**the P value indicates comparison between patients in positive of the two criteria.

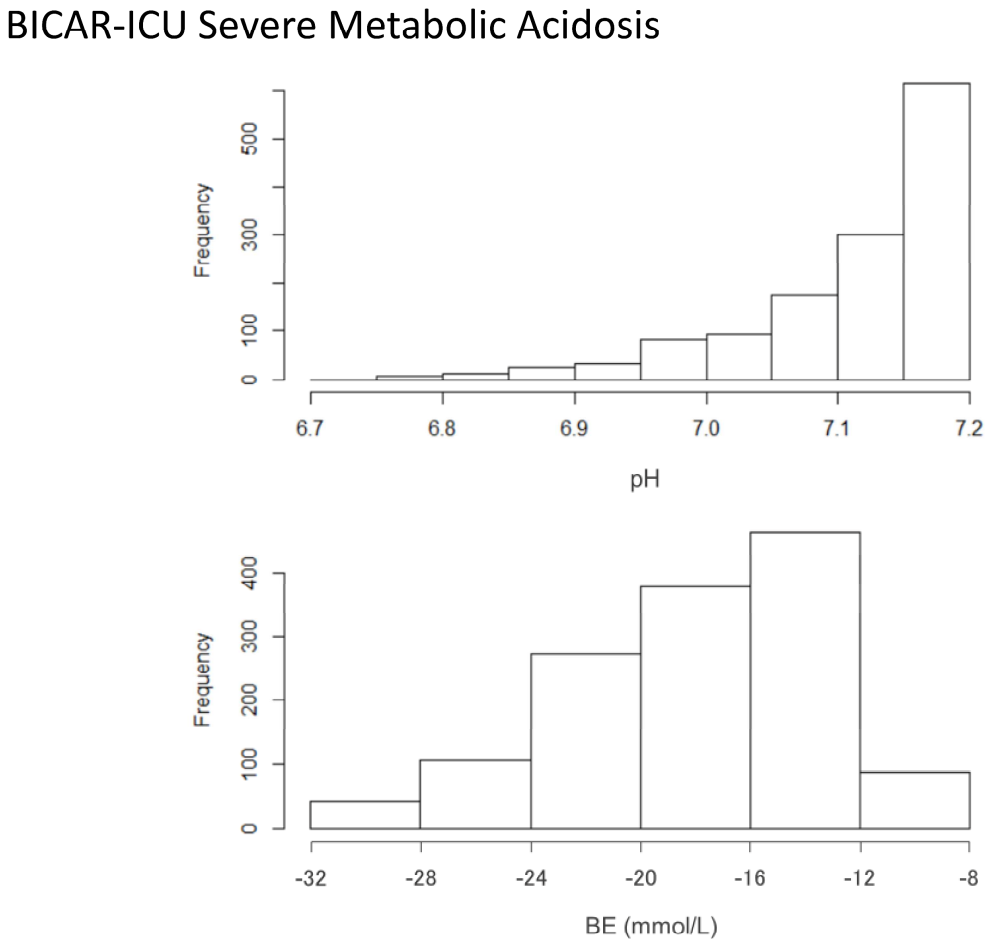

Figure S1. Histogram of pH and base excess on metabolic acidosis diagnosed by the BICAR-ICU criteria

BE: base excess

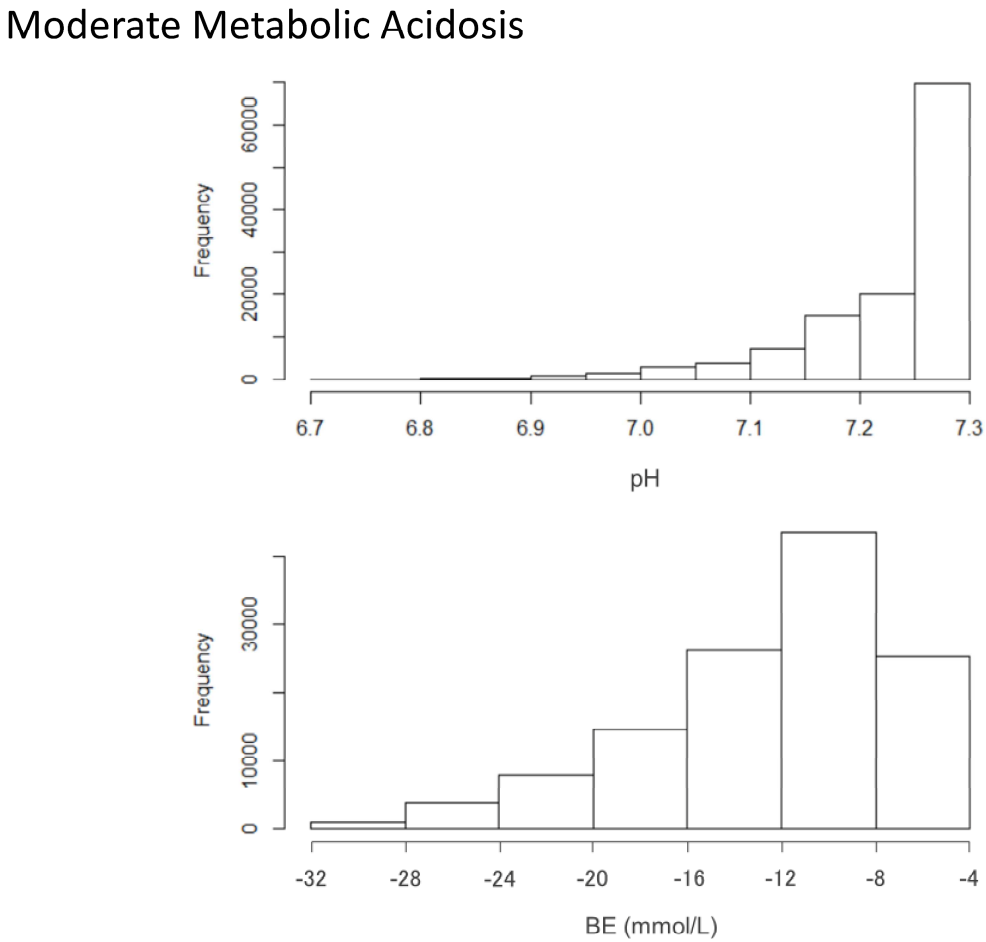

Figure S2. Histogram of pH and base excess on metabolic acidosis diagnosed by the moderate metabolic acidosis criteria

BE: base excess