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ORIGINAL RESEARCH

Associations of the Serum Total Carbon Dioxide Level with Long-Term Clinical Outcomes in Sepsis Survivors

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ABSTRACT

Introduction: Sepsis is characterized by a dysregulated host response to infection that leads to multiple organ dysfunction and often complicated with metabolic acidosis. However, the associations between serum total carbon dioxide level (TCO_2) and long-term clinical outcomes in sepsis survivors remains unknown.

Methods: A total of 7212 sepsis survivors aged ≥ 20 years who were discharged from January 1, 2008 to December 31, 2018 were included in our analyses. The sepsis survivors were further divided into high TCO_2 (≥ 18 mmol/L) and low TCO_2 (< 18 mmol/L) groups, comprising 5023 and 2189 patients, respectively. The following outcomes of interest were included: all-cause mortality, myocardial infarction, ischemic stroke, hospitalization for heart failure, ventricular arrhythmia, and end-stage renal disease (ESRD).

Results: After propensity score matching, the low TCO_2 group was at higher risks of all-cause mortality (hazard ratio [HR] 1.28, 95% confidence interval [95% CI] 1.18–1.39), myocardial infarction (HR 1.83, 95% CI 1.39–2.43), and ESRD (HR 1.38, 95% CI 1.16–1.64) than the high TCO_2 group. The results remained similar after considering death as a competing risk.

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Conclusion: Patients discharged from hospitalization for sepsis have higher risks of worse long-term clinical outcomes. Physicians may need to pay more attention to sepsis survivors whose TCO_2 was low.

Keywords: End-stage renal disease; Myocardial infarction; Sepsis; Sepsis survivor; Serum total carbon dioxide level

Key Summary Points

Why carry out this study?

Metabolic acidosis is frequently found in patients with sepsis, and an understanding of serum total carbon dioxide levels (TCO_2) in sepsis and their long-term clinical outcomes may give us an insight into the role of acid–base status in these patients.

This cohort study assessed the long-term clinical outcomes among sepsis survivors with high and low TCO_2 using propensity score matching to balance clinical characteristics at baseline.

What was learned from this study?

Our study assessed the relationship between serum TCO_2 levels and the risk of all-cause mortality, major adverse cardiovascular events (MACEs), and end-stage renal disease (ESRD) in survivors of sepsis.

In this cohort, sepsis survivors with low TCO_2 levels were associated with increased risks of all-cause mortality, MACEs, and progression to ESRD. This result was consistently significant after considering death as a competing risk.

INTRODUCTION

Sepsis is a major global healthcare concern characterized by a dysregulated host response to infection that can lead to life-threatening multiple organ dysfunction, and it has a high incidence and mortality rate [1–3]. Immune activation in sepsis may lead to systemic inflammation, endothelial barrier dysfunction, exaggerated coagulopathy, fibrin clot formation, myocardial depression, renal dysfunction, and the risk of future adverse events [1, 4–6]. About 37 million incident cases of sepsis and 11 million deaths attributable to this condition (20% of all global deaths) were recorded worldwide in 2017 [7]. In recent years, with the advancement of care technology, earlier recognition, and more effective protocolized treatment, sepsis has become a less life-threatening disorder [8, 9]. However, it remains associated with long-term critical consequences, including chronic inflammation, late immunosuppressive effects, tissue wasting, and organ sequalae [10–13]. Moreover, sepsis survivors (those discharged alive from hospitalization for sepsis) have a sustained increased risk of mortality and higher risks of major adverse cardiac events (MACEs) and long-term functional deficits [14–16].

Metabolic acidosis, a common acid–base disorder indicated by low serum bicarbonate levels, is frequently found in patients with severe sepsis and septic shock [17]. It may cause a reduction in cardiac contractility, release catecholamines, activate the sympathetic system, have a direct arteriolar vasodilatory effect due to increased nitric oxide production, and result in negative bone metabolism and protein balances [17, 18]. The serum bicarbonate and total carbon dioxide (TCO_2) concentrations are both indicators of metabolic acidosis, and can be used interchangeably because bicarbonate ions make up about 95% of the plasma TCO_2 [19]. As serum TCO_2 measurement is usually included in routine chemistry analysis, these values are more available than values for other indicators of metabolic acidosis [20].

A low serum bicarbonate level is an independent risk factor for the progression of kidney disease and has been associated with all-cause mortality in people with chronic kidney disease (CKD) [21–23]. In the third National Health and Nutrition Examination Survey, low serum bicarbonate levels were associated with a 1.74-fold higher risk of all-cause mortality [21]. The Chronic Renal Insufficiency Cohort (CRIC)

study, which enrolled 3939 patients with CKD, demonstrated that increased serum bicarbonate level associated with lower risk of end-stage renal disease (marked by the initiation of dialysis therapy or kidney transplantation) or a 50% reduction in the estimated glomerular filtration rate (eGFR) [22]. A recent retrospective cohort study showed that the serum TCO_2 level was a prognostic factor for 28-day mortality among patients with sepsis [24]. However, that study was limited by the examination of the endpoint of short-term mortality; associations of the TCO_2 concentration with long-term clinical outcomes in sepsis survivors remain unknown. Thus, we conducted a cohort study with a 10-year study period to determine whether the TCO_2 level is associated with risks of long-term adverse outcomes (all-cause mortality, myocardial infarction, ischemic stroke, heart failure, ventricular arrhythmia, and adverse renal outcomes) in sepsis survivors.

METHODS

Data Source

This retrospective cohort study was conducted with medical records data from the Big Data Center of Taipei Veterans General Hospital, which contains comprehensive medical records, pharmacy orders, laboratory results, and examination reports for all inpatients, outpatients, and emergency patients [25]. All patients were aged ≥ 20 years and had had their peripheral venous TCO_2 levels measured within 1 week of discharge from hospitalization for sepsis (international classification of diseases [ICD] code 038, 995.91, A40, and A41), severe sepsis (ICD code 995.92 and R65.20), or septic shock (ICD code 785.52 and R65.21) between 1 January 2008 and 31 December 2018 [26, 27]. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Ethical approval for this study was obtained from the Ethical Committee of Taipei Veterans General (2017-09-002BC), and the study was conducted under the relevant guidelines and regulations. Informed consent was waived because de-identified data were analyzed.

Study Cohort

On the basis of their post-discharge TCO_2 levels, the sepsis survivors were divided into high TCO_2 (≥ 18 mmol/L) and low TCO_2 (< 18 mmol/L) groups. The following baseline variables were recorded: age, sex, eGFR, sources of infection, septic shock, intensive care unit admission, use of mechanical ventilation, use of inotropes, hypertension, coronary artery disease, diabetes mellitus, congestive heart failure, autoimmune disease, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, malignancy, Charlson comorbidity index (CCI) score, use of calcium channel blockers, alpha blockers, beta blockers, renin–angiotensin–aldosterone system inhibitors, diuretics, statins, non-steroidal anti-inflammatory drugs, proton pump inhibitors, antiplatelets, and anticoagulants.

Outcomes

The outcomes of interest were all-cause mortality, myocardial infarction, ischemic stroke, hospitalization for heart failure, ventricular arrhythmia, and end-stage renal disease (defined as eGFR < 15 mL/min/1.73 m^2, initiation of long-term dialysis, or kidney transplantation). All sepsis survivors were followed until death or the end of the study period.

Statistical Analysis

Among the baseline characteristics, categorical variables such as sex, underlying comorbidities, and medications were compared between groups using chi-squared tests. Continuous variables were compared using Student's *t* test for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. We performed multivariate imputation by chained equations to impute missing values with five imputed data sets and 50 iterations [28, 29]. For matched cohort analysis, we used 1:2 propensity score matching of individuals from the low and high TCO_2 groups [30, 31]. The covariates used in the propensity score were as follows: age, sex, eGFR,

respiratory infection, bacteremia, endocarditis, central nervous system infection, skin infection, pelvic inflammatory disease, genitourinary tract infection, intra-abdominal infection, septic shock, intensive care unit admission, use of mechanical ventilation, inotropes use, hypertension, coronary artery disease, diabetes mellitus, congestive heart failure, autoimmune disease, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, malignancy, CCI score, calcium channel blockers, alpha blockers, beta blockers, renin–angiotensin–aldosterone system inhibitors, diuretics, statins, nonsteroidal anti-inflammatory drugs, proton-pump inhibitors, antiplatelets, anticoagulants, and follow-up period. In addition, we calculated propensity scores for the likelihood of sepsis survivors with high and low TCO_2 by including clinical covariates in a multivariate logistic regression model (Table S1 in the supplementary material). The standardized mean difference was calculated to assess the balance between sepsis survivors with high and low TCO_2 after matching, and a difference of less than 0.1 in the score was considered to be well balanced [32, 33]. Cox regression was used to obtain hazard ratios (HRs) for the evaluation of relative risks of outcomes in the two study groups. All analyses were performed using the SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA) and R software (version 3.5.2 for Windows; R Foundation for Statistical Computing, Vienna, Austria. The significance level was set to $p < 0.05$.

RESULTS

Baseline Characteristics of Study Population

The study cohort comprised 7212 sepsis survivors allocated to the low (n = 2189) and high (n = 5023) TCO_2 groups before propensity score matching. The baseline characteristics of the study subjects are provided in Table 1. Relative to those in the high TCO_2 group, patients in the low TCO_2 group were younger, and used more inotropes and proton pump inhibitors. Respiratory and genitourinary tract infections were less frequent, and intra-abdominal infection was more frequent, in the low TCO_2 group than in the high TCO_2 group. There was no missing data for age, sex, underlying comorbidities, and medications, but there were missing values in the eGFR (proportions of missing values 8.8%). Propensity score matching yielded a matched cohort of 3414 sepsis survivors (2276 patients in the high TCO_2 group and 1138 patients in the low TCO_2 group). Baseline characteristics did not differ significantly between these groups. After propensity score matching, the median age of matched-cohort was 80.8 (interquartile range [IQR] 67.7–87.1) years; 32.4% of patients were women, and the median eGFR was 63.1 (IQR 32.8–92.9) ml/min/1.73 m^2, and the baseline characteristics were well balanced between these two groups (Fig. S1 in the supplementary material).

Long-Term Risks of Mortality, MACEs, and End-Stage Renal Disease According to TCO_2 Levels

During the study period, the low TCO_2 group had higher risks of all-cause mortality [HR 1.28; 95% confidence interval (CI) 1.18–1.39; $p < 0.001$], myocardial infarction (HR 1.83; 95% CI 1.39–2.43; $p < 0.001$), and end-stage renal disease (HR 1.38; 95% CI 1.16–1.64; $p < 0.001$; Table 2). No significant difference in the ischemic stroke, hospitalization for heart failure, or ventricular arrhythmia risk was observed between groups. The results remained similar after considering death as a competing risk. The cumulative incidences of all-cause mortality, myocardial infarction, ischemic stroke, and end-stage renal disease are illustrated in Fig. 1.

Subgroup Analyses for Risks of All-Cause Mortality and Clinical Outcomes Stratified by Septic Shock Status

In the subgroup analysis stratified by with and without septic shock, the effects of serum TCO_2 on all-cause mortality (P for interaction = 0.122), myocardial infarction (P for interaction = 0.956), ischemic stroke (P for

Table 1 Baseline characteristics of the study population before and after propensity score matching among sepsis survivors with high and low TCO_2

	Before propensity score matching				After propensity score matching			
	All patients (n = 7212)	High TCO_2 group (n = 5023)	Low TCO_2 group (n = 2189)	SMD	All patients (n = 3414)	High TCO_2 group (n = 2276)	Low TCO_2 group (n = 1138)	SMD
Age, years	80.2 [66.4, 86.8]	80.7 [67.4, 87.1]	79.1 [64.1, 85.8]	0.145	80.8 [67.7, 87.1]	80.9 [67.4, 87.1]	80.8 [68.3, 87.1]	0.009
Female sex	2311 (32.0)	1604 (31.9)	707 (32.3)	0.008	1105 (32.4)	721 (31.7)	384 (33.7)	0.044
eGFR, mL/min/1.73 m^2	58.4 [26.7, 93.6]	68.0 [34.6, 100.7]	38.5 [17.5, 72.8]	0.428	63.1 [32.8, 92.9]	65.0 [34.9, 93.2]	59.3 [28.6, 91.7]	0.048
Sources of infection								
Respiratory infection	4616 (64.0)	3429 (68.3)	1187 (54.2)	0.291	2327 (68.2)	1534 (67.4)	793 (69.7)	0.049
Bacteremia	646 (9.0)	511 (10.2)	135 (6.2)	0.147	331 (9.7)	225 (9.9)	106 (9.3)	0.019
Endocarditis	118 (1.6)	87 (1.7)	31 (1.4)	0.025	48 (1.4)	35 (1.5)	13 (1.1)	0.034
CNS infection	106 (1.5)	76 (1.5)	30 (1.4)	0.012	48 (1.4)	30 (1.3)	18 (1.6)	0.022
Skin infection	800 (11.1)	578 (11.5)	222 (10.1)	0.044	384 (11.2)	259 (11.4)	125 (11.0)	0.013
PID	63 (0.9)	43 (0.9)	20 (0.9)	0.006	31 (0.9)	19 (0.8)	12 (1.1)	0.023
GU tract infection	1097 (15.2)	885 (17.6)	212 (9.7)	0.233	514 (15.1)	342 (15.0)	172 (15.1)	0.002
IAI	1968 (27.3)	1299 (25.9)	669 (30.6)	0.105	900 (26.4)	603 (26.5)	297 (26.1)	0.009
Septic shock	1726 (23.9)	1204 (24.0)	522 (23.8)	0.003	813 (23.8)	549 (24.1)	264 (23.2)	0.022
ICU admission	5448 (75.5)	3659 (72.8)	1789 (81.7)	0.213	2550 (74.7)	1703 (74.8)	847 (74.4)	0.009
Mechanical ventilation	3836 (53.2)	2420 (48.2)	1416 (64.7)	0.338	1724 (50.5)	1159 (50.9)	565 (49.6)	0.025
Inotropes use	5647 (78.3)	3728 (74.2)	1919 (87.7)	0.348	2721 (79.7)	1817 (79.8)	904 (79.4)	0.010
Underlying comorbidities								
Hypertension	5500 (76.3)	3941 (78.5)	1559 (71.2)	0.167	2700 (79.1)	1791 (78.7)	909 (79.9)	0.029
CAD	2115 (29.3)	1473 (29.3)	642 (29.3)	< 0.001	1035 (30.3)	708 (31.1)	327 (28.7)	0.052
Diabetes mellitus	2425 (33.6)	1711 (34.1)	714 (32.6)	0.031	1173 (34.4)	769 (33.8)	404 (35.5)	0.036

Table 1 continued

	Before propensity score matching				After propensity score matching			
	All patients (n = 7212)	**High TCO_2 group (n = 5023)**	**Low TCO_2 group (n = 2189)**	**SMD**	**All patients (n = 3414)**	**High TCO_2 group (n = 2276)**	**Low TCO_2 group (n = 1138)**	**SMD**
CHF	1990 (27.6)	1475 (29.4)	515 (23.5)	0.133	989 (29.0)	650 (28.6)	339 (29.8)	0.027
Autoimmune disease	245 (3.4)	173 (3.4)	72 (3.3)	0.009	122 (3.6)	77 (3.4)	45 (4.0)	0.030
COPD	1074 (14.9)	822 (16.4)	252 (11.5)	0.140	542 (15.9)	367 (16.1)	175 (15.4)	0.021
OSAS	609 (8.4)	457 (9.1)	152 (6.9)	0.079	310 (9.1)	210 (9.2)	100 (8.8)	0.015
Malignancy	3659 (50.7)	2595 (51.7)	1064 (48.6)	0.061	1814 (53.1)	1220 (53.6)	594 (52.2)	0.028
CCI score	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]	0.110	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]	0.027
Medications								
CCBs	4175 (57.9)	3030 (60.3)	1145 (52.3)	0.162	2064 (60.5)	1374 (60.4)	690 (60.6)	0.005
Alpha blockers	2959 (41.0)	2138 (42.6)	821 (37.5)	0.103	1454 (42.6)	970 (42.6)	484 (42.5)	0.002
Beta blockers	3721 (51.6)	2689 (53.5)	1032 (47.1)	0.128	1878 (55.0)	1242 (54.6)	636 (55.9)	0.027
RAASis	3498 (48.5)	2528 (50.3)	970 (44.3)	0.121	1751 (51.3)	1175 (51.6)	576 (50.6)	0.020
Diuretics	5751 (79.7)	4096 (81.5)	1655 (75.6)	0.145	2771 (81.2)	1860 (81.7)	911 (80.1)	0.042
Statins	1719 (23.8)	1227 (24.4)	492 (22.5)	0.046	879 (25.7)	587 (25.8)	292 (25.7)	0.003
NSAIDs	4661 (64.6)	3386 (67.4)	1275 (58.2)	0.190	2329 (68.2)	1562 (68.6)	767 (67.4)	0.026
PPIs	5492 (76.2)	3745 (74.6)	1747 (79.8)	0.125	2606 (76.3)	1733 (76.1)	873 (76.7)	0.013
Antiplatelets	3167 (43.9)	2290 (45.6)	877 (40.1)	0.112	1541 (45.1)	1028 (45.2)	513 (45.1)	0.002

Table 1 continued

	Before propensity score matching				After propensity score matching			
	All patients (n = 7212)	High TCO_2 group (n = 5023)	Low TCO_2 group (n = 2189)	SMD	All patients (n = 3414)	High TCO_2 group (n = 2276)	Low TCO_2 group (n = 1138)	SMD
Anticoagulants	851 (11.8)	635 (12.6)	216 (9.9)	0.088	440 (12.9)	304 (13.4)	136 (12.0)	0.042

Data are presented as n (%) or median [interquartile range]

TCO_2 total carbon dioxide, *SMD* standardized mean difference, *eGFR* estimated glomerular filtration rate, *CNS* central nervous system, *PID* pelvic inflammatory disease, *GU* genitourinary, *IAI* intra-abdominal infection, *ICU* intensive care unit, *CAD* coronary artery disease, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *OSAS* obstructive sleep apnea syndrome, *CCI* Charlson comorbidity index, *CCBs* calcium channel blockers, *RAASis* renin–angiotensin–aldosterone system inhibitors, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PPIs* proton pump inhibitors

interaction = 0.753), hospitalization for heart failure (P for interaction = 0.941), ventricular arrhythmia (P for interaction = 0.638), and end-stage renal disease (P for interaction = 0.794) were consistent across patient subgroups (Table 3).

DISCUSSION

In this study, we demonstrated that lower serum TCO_2 levels were associated with greater risks of adverse long-term outcomes in sepsis survivors. Patients with low TCO_2 levels were at greater risk of all-cause mortality, myocardial infarction, and end-stage renal disease than were those with high TCO_2 levels over a 10-year study period.

Cardiovascular events are considered to be important contributors to increased long-term mortality in sepsis survivors. Yende et al. [15] conducted a large retrospective cohort analysis with 4179 sepsis survivors and 819,283 control subjects, demonstrating that sepsis survivors had a 1.9-fold higher risk of the 1-year incidence of cardiovascular events (stroke, myocardial infarction, coronary revascularization, and transient ischemic attack) relative to matched-population control subjects.

Accumulating evidence identifies acidosis as a contributor to the progression of kidney disease in people with CKD [21, 22]. The multicenter prospective observational CRIC study, which included 3939 participants with CKD stages 2–4 followed for a median of 3.9 years, demonstrated that each 1-mEq/L increase in the serum bicarbonate level was associated with a 3% reduced risk of a composite renal outcome (eGFR decline $\geq$ 50% or eGFR $<$ 15 mL/min/1.73 m^2) [22]. However, the serum bicarbonate level was not associated significantly with all-cause mortality or atherosclerotic cardiovascular events (myocardial infarction, stroke, and peripheral arterial disease). Patients with diabetes were not excluded from the CRIC study, as has been done in other studies, and accounted for nearly half of the study population. Diabetes, a cardiovascular risk equivalent, may influence the interaction between the serum bicarbonate level and mortality. In a retrospective observational cohort study including 5422 patients, serum bicarbonate levels $\leq$ 22 mmol/L were associated with a 54% increased risk of kidney disease progression compared with serum bicarbonate levels of 25–26 mmol/L [21]. Nadir serum bicarbonate levels ($<$ 18 mmol/L) in patients on hemodialysis were also associated with a greater mortality risk than were levels of 18–23 mmol/L [34]. Consistent with these findings, low serum TCO_2 levels were associated with a higher mortality rate and worse renal outcomes among sepsis survivors in this study.

Kim et al. [24] concluded that serum TCO_2 levels $<$ 20 mEq/L correlated with 28-day mortality in patients with sepsis. However, that study was limited by the examination of short-term mortality as the endpoint. The use of 28-day outcomes in clinical studies may lead to

Table 2 Risks of all-cause mortality and clinical outcomes among sepsis survivors with high and low TCO_2

Outcome	No. of events	Person-years	Incidence rate[a]	Propensity score-matched		Competing risk for mortality	
				HR (95% CI)	*p* value	HR (95% CI)	*p* value
All-cause mortality							
High TCO_2 group	1550	2878	53.86	Reference		–	
Low TCO_2 group	846	1469	57.59	1.28 (1.18–1.39)	< 0.001	–	
Myocardial infraction							
High TCO_2 group	114	2708	4.21	Reference		Reference	
Low TCO_2 group	87	1368	6.36	1.83 (1.39–2.43)	< 0.001	1.55 (1.17–2.05)	0.002
Ischemic stroke							
High TCO_2 group	88	2720	3.24	Reference		Reference	
Low TCO_2 group	40	1397	2.86	1.04 (0.72–1.51)	0.833	0.89 (0.62–1.30)	0.560
Hospitalization for heart failure							
High TCO_2 group	463	2326	19.91	Reference		Reference	
Low TCO_2 group	207	1235	16.76	1.06 (0.90–1.25)	0.480	0.90 (0.77–1.06)	0.220
Ventricular arrhythmia							
High TCO_2 group	94	2712	3.47	Reference		Reference	
Low TCO_2 group	50	1410	3.55	1.25 (0.89–1.76)	0.204	1.07 (0.76–1.50)	0.720
End-stage renal disease							
High TCO_2 group	358	2393	14.96	Reference		Reference	
Low TCO_2 group	206	1222	16.86	1.38 (1.16–1.64)	< 0.001	1.19 (1.01–1.42)	0.042

TCO_2 total carbon dioxide, *No.* numbers, *HR* hazard ratio, *CI* confidence interval
[a]Per 100 person-years

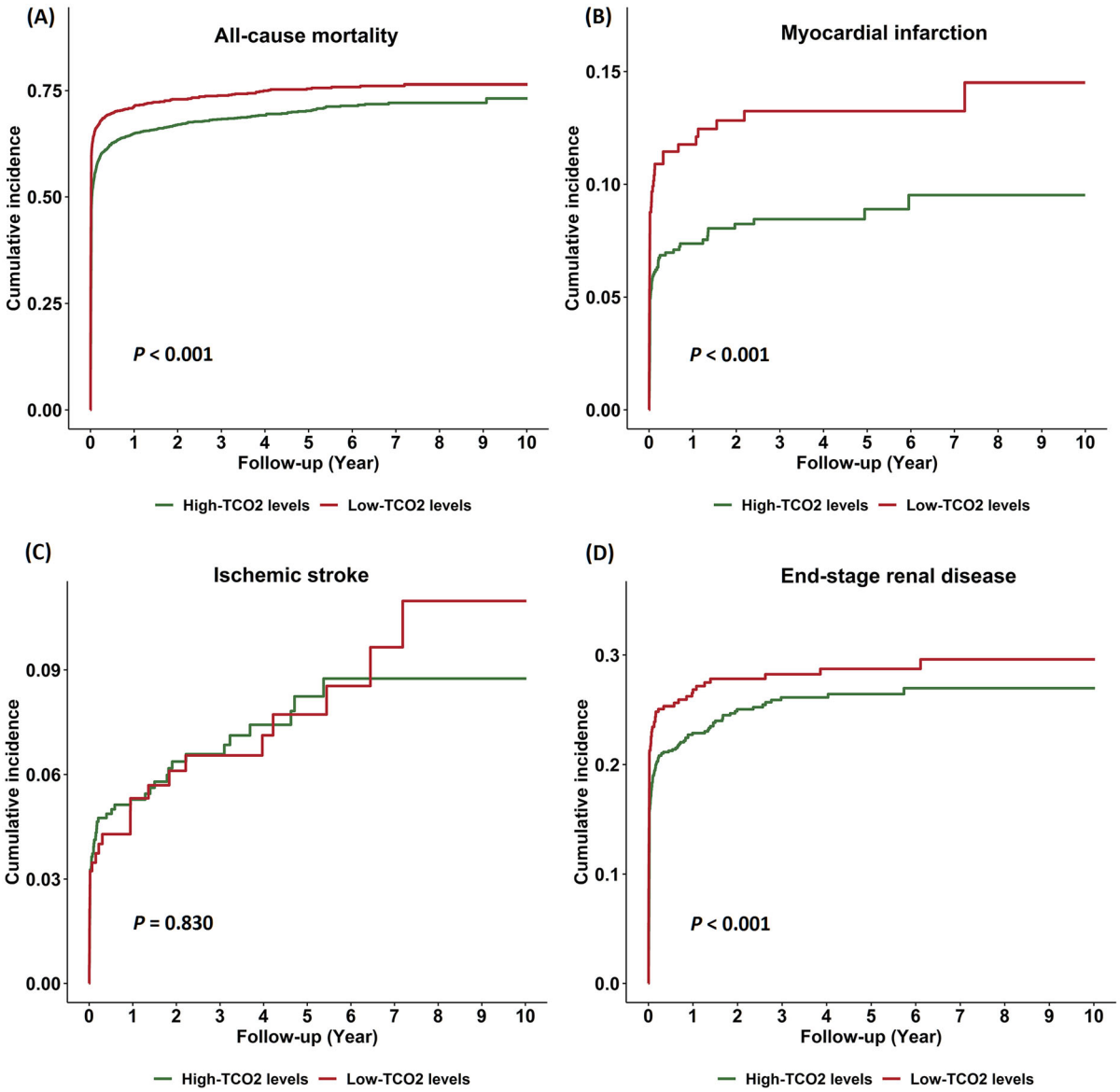

Fig. 1 Kaplan–Meier curves for the risks of **a** all-cause mortality, **b** myocardial infarction, **c** ischemic stroke, and **d** end-stage renal disease among sepsis survivors with high and low TCO_2. *TCO_2* total carbon dioxide

the underestimation of morbidity and mortality, and the drawing of inaccurate inferences. The present study showed that the serum TCO_2 level is a predictor of mortality in patients with sepsis over a longer follow-up period.

The pathophysiology underlying this association between low TCO_2 level and long-term outcome in sepsis survivors remains unknown. Low TCO_2 level commonly indicates metabolic acidosis and would be a surrogate of renal dysfunction, which had been shown to be associated with cardiovascular events and long-term mortality. Metabolic acidosis is associated with the development of cardiovascular disease due to its several detrimental effects on the cardiovascular system, such as induced inflammation, activation of the renin–angiotensin–aldosterone system, and insulin resistance. Inflammation associated with metabolic acidosis may result in endothelial

Table 3 Risks of all-cause mortality and clinical outcomes among sepsis survivors with high and low TCO_2 stratified by with and without septic shock

Outcome	No. of events	Person-years	Incidence rate[a]	Propensity score-matched		Competing risk for mortality	
				HR (95% CI)	*p* value	HR (95% CI)	*p* value
Patients without septic shock							
All-cause mortality*							
High TCO_2 group	1197	2517	47.56	Reference		–	–
Low TCO_2 group	645	1354	47.64	1.21 (1.10–1.33)	< 0.001	–	–
Myocardial infraction[§]							
High TCO_2 group	86	2362	3.64	Reference		Reference	
Low TCO_2 group	66	1265	5.22	1.75 (1.27–2.41)	0.001	1.54 (1.12–2.13)	0.008
Ischemic stroke[‖]							
High TCO_2 group	118	2290	5.15	Reference		Reference	
Low TCO_2 group	45	1261	3.57	0.85 (0.60–1.19)	0.339	1.00 (0.67–1.52)	0.980
Hospitalization for heart failure[¶]							
High TCO_2 group	334	2058	16.23	Reference		Reference	
Low TCO_2 group	160	1129	14.18	1.08 (0.90–1.31)	0.406	0.96 (0.79–1.15)	0.640
Ventricular arrhythmia**							
High TCO_2 group	85	2363	3.60	Reference		Reference	
Low TCO_2 group	45	1299	3.46	1.18 (0.82–1.70)	0.366	1.05 (0.73–1.51)	0.790
End-stage renal disease[††]							
High TCO_2 group	246	2100	11.71	Reference		Reference	
Low TCO_2 group	162	1126	14.39	1.51 (1.24–1.84)	< 0.001	1.36 (1.12–1.66)	0.002
Patients with septic shock							
All-cause mortality*							

Table 3 continued

Outcome	No. of events	Person-years	Incidence rate[a]	Propensity score-matched		Competing risk for mortality	
				HR (95% CI)	*p* value	HR (95% CI)	*p* value
High TCO_2 group	353	361	97.77	Reference		–	–
Low TCO_2 group	201	115	174.69	1.59 (1.33–1.89)	< 0.001	–	–
Myocardial infraction[§]							
High TCO_2 group	28	346	8.08	Reference		Reference	
Low TCO_2 group	21	103	20.3	2.14 (1.21–3.78)	0.009	1.59 (0.90–2.79)	0.110
Ischemic stroke[‖]							
High TCO_2 group	34	328	10.36	Reference		Reference	
Low TCO_2 group	8	112	7.15	0.61 (0.28–1.33)	0.216	0.55 (0.23–1.35)	0.200
Hospitalization for heart failure[¶]							
High TCO_2 group	129	268	48.08	Reference		Reference	
Low TCO_2 group	47	106	44.16	1.01 (0.72–1.41)	0.965	0.76 (0.54–1.06)	0.110
Ventricular arrhythmia[**]							
High TCO_2 group	9	350	2.57	Reference		Reference	
Low TCO_2 group	5	111	4.52	1.70 (0.57–5.10)	0.340	1.15 (0.39–3.39)	0.800
End-stage renal disease[††]							
High TCO_2 group	112	293	38.22	Reference		Reference	
Low TCO_2 group	44	96	45.99	1.10 (0.77–1.55)	0.611	0.83 (0.58–1.18)	0.290

TCO_2 total carbon dioxide, *No.* numbers, *HR* hazard ratio, *CI* confidence interval

[*]*P* for interaction = 0.122; [§]*P* for interaction = 0.956; [‖]*P* for interaction = 0.753; [¶]*P* for interaction = 0.941; [**]*P* for interaction = 0.638; [††]*P* for interaction = 0.794

[a]Per 100 person-years

dysfunction and an increased risk of cardiovascular events [35–37]. Metabolic acidosis is associated with elevated endothelin and aldosterone levels due to the activation of the renin–angiotensin–aldosterone system [38, 39]. Metabolic acidosis also increases insulin resistance, which may contribute to the pathogenesis of cardiovascular disease [40, 41]. However, further prospective studies are warranted to clarify the causality.

The strengths of the present study include the examination of a large cohort of sepsis survivors over a study period of 10 years. In addition, we investigated associations between the serum TCO_2 level and not only all-cause mortality but also adverse cardiovascular outcomes in sepsis survivors. To our knowledge, this study is the first to examine serum TCO_2 levels measured after discharge from hospitalization for sepsis, rather than those measured on admission. However, some limitations of this study must be considered. First, the study was observational, and thus may have been affected by selection bias and unmeasured confounding factors; in addition, no inference about causality could be made. Second, we did not have access to partial CO_2 pressure or pH measurements for the study participants and cannot exclude the possibility that some of the variation in the bicarbonate levels represented respiratory effects. Additionally, we did not have information on the use of alkali therapy, which may influence the TCO_2 level. Finally, long-term clinical outcomes were obtained using linkage to the hospital registry database of the Big Data Center. It is possible that some people may be lost to follow-up during the study period. However, sepsis survivors are a fragile population that requires continued access to medical resources for treatment and the study participants are old, leading to the relatively low possibility of those who do not continue to be followed up at a medical center like our hospital or move to another city.

CONCLUSION

The sepsis survivors with low serum TCO_2 level were associated with higher risks of mortality, myocardial infarction, and end-stage renal disease. Prospective studies are needed to confirm these relationships and to evaluate associations between the serum TCO_2 level and adverse long-term outcomes.

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Compliance with Ethics Guidelines. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Ethical approval for this study was obtained from the Ethical Committee of Taipei Veterans General (2017-09-002BC), and the study was conducted under the relevant guidelines and regulations. Informed consent was waived because de-identified data were analyzed.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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