Original Article

Impact of abdominal aortic calcification on 90-day mortality in sepsis patients: a pilot retrospective cohort study

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Aim: We aimed to investigate the association between aortic calcification and 90-day mortality in sepsis patients admitted to the intensive care unit.

Methods: We evaluated adult patients (≥18 years) diagnosed with sepsis based on the Sepsis-3 criteria and admitted to our intensive care unit between April 2011 and March 2015. They were classified according to the degree of abdominal aortic calcification (severe and non-severe), grouped per age (<65, 65–75, and >75 years), and matched. Survival curves were generated, and between-group differences were evaluated.

Results: Overall, 164 patients were included. The Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores were not significantly different between the severity groups, whereas there were significant differences in age ($P < 0.001$), sex ($P = 0.017$), and presence of diabetes mellitus ($P < 0.001$), hypertension ($P < 0.001$), dyslipidemia ($P = 0.048$), and maintenance dialysis ($P = 0.001$). The severe abdominal aortic calcification group showed significantly poorer prognosis than the non-severe group (log–rank $P = 0.009$). The adjusted odds ratio of severe calcification was the highest in patients aged <65 years (7.167; 95% confidence interval, 1.042–49.28, $P = 0.045$). Twenty-eight patients from each group were matched. The 90-day survival rate of the severe calcification group remained significantly lower than that of the non-severe calcification group (53.6% [15/28] versus 82.1% [23/28], $P = 0.022$).

Conclusions: Severe abdominal aortic calcification is associated with the 90-day mortality of sepsis patients, particularly among those aged <65 years. Thus, caution is necessary in patients younger than 65 years; they may need to be treated with as much care as the elderly.

Key words: Abdominal aorta, mortality, prognosis, sepsis, vascular calcification

INTRODUCTION

SEPSIS IS THE leading cause of global health loss, accounting for 19.7% of deaths in 2017.[1] In 2016, sepsis was redefined as "a life-threatening organ dysfunction caused by a dysregulated host response to infection."[2] Infections were classified according to clinical outcomes as those with poor (i.e., leading to mortality) and good prognosis, with more research focused on the former.[2]

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Age is associated with decreased host responses and organ dysfunction. Accordingly, many epidemiological studies on mortality report age to be an important influencing factor. Organ damage resulting from age-related microcirculatory dysfunction and immune response is directly associated with death.[3] Furthermore, aging majorly affects the development of sepsis and substantially contributes to increased mortality.[3]

Calcification is an age-related change in blood vessels that is accelerated by diabetes mellitus (DM),[4] hypertension,[5] and chronic kidney disease (CKD).[6] The incidence of arterial calcification increases with age, and >90% of men and 67% of women older than 70 years can experience arterial calcification.[7] The development of vascular calcification is highly regulated, involving vascular smooth muscle cells and recapitulated skeletal bone formation, which occur following the loss of calcification inhibitors, DNA damage-response signaling, and apoptosis.[7] Abdominal aortic

calcification (AAC), measured using computed tomography (CT), is a strong predictor of future cardiovascular events[8] and all-cause mortality in dialysis[9] and CKD patients.[10] Furthermore, it is associated with a high risk of major fragility fractures.[11] However, the prognostic impact of aortic calcification in sepsis patients remains unclear. Thus, this study aimed to examine the relationship between aortic calcifications and 90-day mortality in sepsis patients, regardless of infection site, with some organ failure admitted to the intensive care unit (ICU).

METHODS

Study design and patients

THIS WAS A single-center retrospective cohort study of adult patients (age ≥ 18 years) diagnosed with sepsis based on the Sepsis-3 criteria[2] and admitted to our ICU between April 2011 and March 2015. Sepsis-3 was retrospectively diagnosed based on clinical records. Only patients who underwent abdominal CT 2 weeks before and after admission were included. The patients were grouped according to the degree of AAC (severe and non-severe) and age (<65, 65–75, and >75 years).

Assessment of calcification

The definition of the degree of calcification was partially modified from that by Tatami *et al.*[10] as follows (Fig. S1): (i) abdominal CT images were obtained with a slice thickness of 5 mm, and the aorta from the diaphragmatic orifice to the common iliac artery bifurcation was included in the measurements, (ii) the slice with the most severe calcification was selected visually, (iii) in each slice, the transverse section of the aorta was considered as one circle, (iv) the extent of the calcified aortic wall was visually determined as a percentage of the circle divided into five categories, i.e., 0%, ≤25%, ≤50%, ≤75%, or ≤100%. The extent of calcification was accordingly referred to as the AAC ratio (AACR), with 0%, ≤25%, ≤50%, ≤75%, and ≤100% categorized as AACR 0, 1, 2, 3, and 4, respectively. Severe calcification was defined as an AACR of 4.

Data collection

Pre-identified pseudoanonymized data for analysis were collected from the hospital's clinical information system and included demographic characteristics, sepsis severity scores (Acute Physiology and Chronic Health Evaluation [APACHE] II score and Sequential Organ Failure Assessment [SOFA] score), and comorbidities (DM, hypertension, maintenance dialysis, dyslipidemia, and positive smoking history). The presence or absence of a pertinent medical history was determined based on an established diagnosis or information on medical treatment. Diabetes mellitus was defined based on hemoglobin A1c (National Glycohemoglobin Standardization Program) >6.5%; hypertension, systolic blood pressure >130 mmHg; dyslipidemia, high-density lipoprotein levels <40 mg/dL, or triglyceride levels >150 mg/dL. Maintenance dialysis was defined as receipt of routine dialysis within the last 3 months. A positive smoking history was defined as active or previous smoking of at least one cigarette per day.

Matched-pair cohort

A matched-pair cohort was used with a propensity score to minimize the effect of confounding factors (e.g., DM) that could lead to biased results. The score was assigned based on the probability of AAC and estimated using a multivariable logistic regression model. A one-to-one nearest neighbor matching algorithm was applied using a caliper width of 0.2 times the standard deviation. The following variables were selected to generate the propensity score: age, DM, hypertension, dyslipidemia, maintenance of dialysis, and a positive smoking history. The area under the curve was calculated by drawing a receiver operating characteristic curve with severe calcification as the outcome using the propensity score.

Statistical analysis

The primary end-point was 90-day mortality. For all significant between-group differences, the odds ratios as per each age group were determined. Univariate analysis was used to determine whether age, sex, and comorbidities influenced 90-day mortality. Continuous variables are expressed as medians (interquartile range) and were compared using the Kruskal–Wallis and Mann–Whitney *U*-tests, as appropriate. Logistic regression analysis was used for the multivariate analysis. Categorical data are expressed as proportions and were compared using the χ^2-test. Survival was estimated by generating survival curves using the Kaplan–Meier method, and between-group differences in survival were evaluated using the log–rank test. A matched-pair cohort was used to minimize the imbalance between groups. All statistical analyses were carried out using Stata 11.2 (Stata Corp., College Station, TX, USA). All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline patient characteristics

AMONG 178 SEPSIS patients, 164 (92.1%) underwent abdominal CT and were included in the analysis (Table 1). There were no significant between-group differences in the SOFA or APACHE II scores, whereas age ($P < 0.001$), sex ($P < 0.001$), DM ($P < 0.001$), hypertension ($P < 0.001$), dyslipidemia ($P = 0.015$), maintenance dialysis ($P = 0.032$), and positive smoking history ($P = 0.003$) were significantly different (Table 1).

Association of calcification and age with 90-day mortality

Figure 1A shows the Kaplan–Meier curves of the AACR groups. Although there were no significant differences among the four groups ($P = 0.133$), the survival rate of the AACR 4 (severe AAC) group tended to be lower than that of the AACR 0–3 (non-severe AAC) groups. Thus, the latter were combined into one group and compared with the AACR 4 group. Comparing baseline patient characteristics before matching showed no significant between-group differences in the SOFA scores ($P = 0.466$), APACHE II scores ($P = 0.599$), or positive smoking history ($P = 0.232$). In contrast, there were significant differences in age ($P < 0.001$), sex ($P = 0.017$), DM ($P < 0.001$), hypertension ($P < 0.001$), dyslipidemia ($P = 0.048$), and maintenance dialysis ($P = 0.001$; Table S1). The severe AAC group had significantly poorer prognosis than the non-severe AAC one (log–rank $P = 0.009$). The cumulative survival rates were 56.2% for the former and 76.2% for the latter (Fig. 1B).

Age-wise (<65, 65–75, and >75 years) subgroup analyses showed that the adjusted odds ratio of AACR 4 was the highest in those aged <65 years (7.167 [95% confidence interval, 1.042–49.28], $P = 0.045$; Fig. 2).

Univariate analysis of factors influencing 90-day mortality

On univariate analysis, age ($P = 0.074$), sex ($P = 0.281$), DM ($P = 0.987$), hypertension ($P = 0.789$), dyslipidemia ($P = 0.265$), maintenance dialysis ($P = 0.654$), and positive smoking history ($P = 0.373$) had no significant effect on the 90-day mortality rate (Table S2).

Outcomes after using a matched-pair cohort

Using the propensity score, the receiver operating characteristic curve with severe calcification as an outcome had an area under the curve of 0.882 ($P < 0.01$), which is a good indicator. In each group, 28 patients were matched in a 1:1 ratio during matched-pair cohort analysis (Table 2). The overall quality of the matched sample was assessed by comparing the standardized difference (Std diff) of the means

Table 1. Characteristics of patients with sepsis admitted to the intensive care unit

	Total (n = 164)	AACR					*P*-value
		0 (n = 28)	1 (n = 41)	2 (n = 17)	3 (n = 29)	4 (n = 49)	
Age (years), median (IQR)	70 (57–77)	40 (34–52.8)	68 (62–75.5)	73 (67–77.5)	74 (66–77.5)	77 (70–81)	<0.001
Sex, % (F/M)	39 (64/100)	60.7 (17/11)	56.1 (23/18)	47.1 (8/9)	13.8 (4/25)	24.5 (12/37)	<0.001
SOFA score, median (IQR)	10 (7–13)	10 (7.3–13)	11 (7–12.5)	10 (7–13)	9 (7.5–12.5)	9 (8–13)	0.832
APACHE II score, median (IQR)	20 (15–27)	22 (16–28)	21 (16–29)	17 (13–27)	19 (15–28)	20 (15–25)	0.967
Comorbidity, *n* (%)							
Diabetes mellitus	46 (28.0)	1 (3.6)	6 (14.6)	2 (11.8)	11 (37.9)	25 (51.0)	<0.001
Hypertension	77 (47.0)	6 (21.4)	16 (39.0)	6 (35.3)	13 (44.8)	36 (73.4)	<0.001
Dyslipidemia	28 (17.1)	0 (0)	4 (9.8)	2 (11.8)	8 (27.6)	12 (24.5)	0.015
Maintenance dialysis	11 (6.7)	1 (3.6)	1 (2.4)	0 (0)	1 (3.4)	8 (16.3)	0.032
Positive history of smoking	34 (20.7)	2 (7.1)	3 (7.3)	4 (23.5)	12 (41.4)	13 (26.5)	0.003

AACR 0–4, abdominal aortic calcifications ratio classified using the Kruskal–Wallis test; APACHE, Acute Physiology and Chronic Health Evaluation; F/M, female-to-male ratio; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

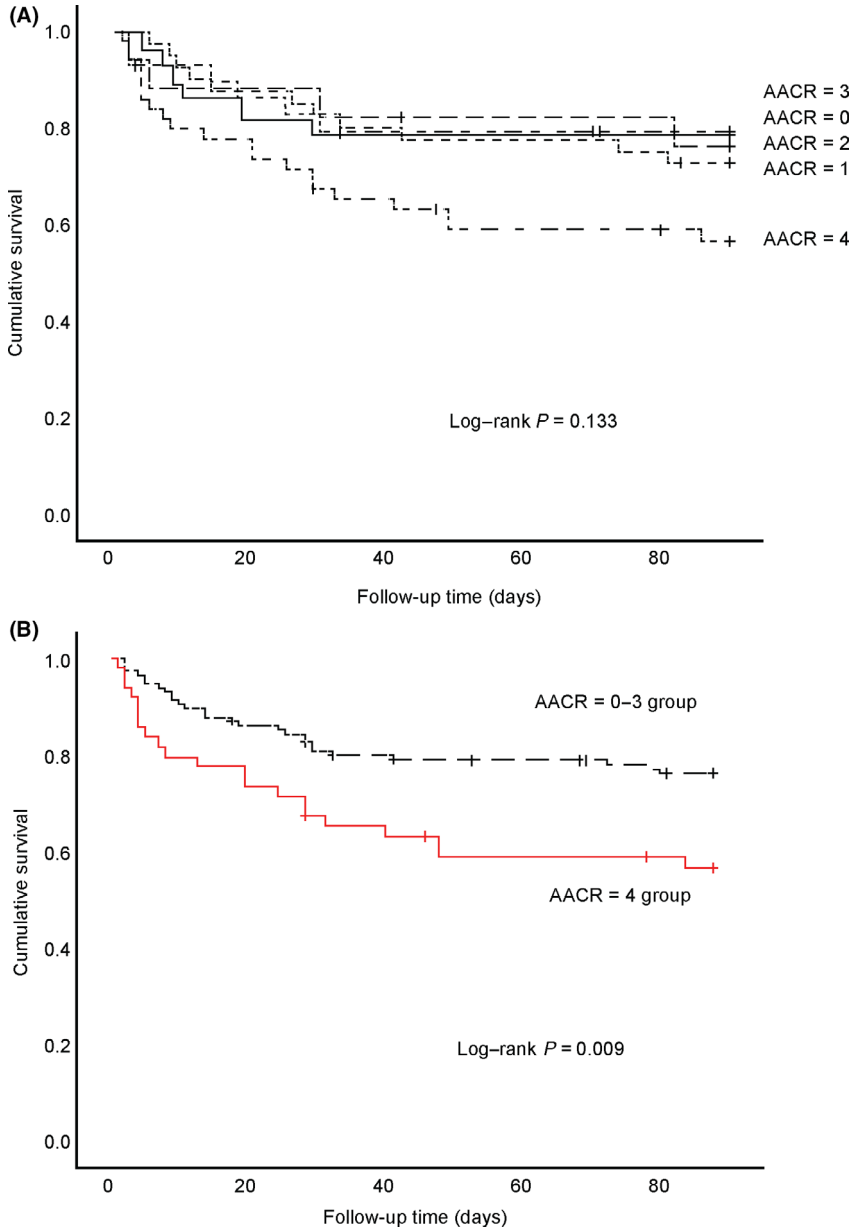

Fig. 1. A, Kaplan–Meier 90-day survival curves for the abdominal aortic calcification ratio (AACR) groups among sepsis patients admitted to the intensive care unit. There were no significant differences in survival rates between the five groups. B, Kaplan–Meier 90-day survival curves of the abdominal aortic calcification ratio groups 0–3 and 4. The AACR 4 group showed a significantly lower survival rate than the AACR 0–3 group (P = 0.009).

and ratio of the variances between the propensity scores of the two groups. There were no significant differences in the mean age (74 versus 75.5 years, P = 0.951, Std diff = 0.0018), SOFA score (median 9 versus 9, P = 0.592, Std diff = 0.0314), APACHE II score (median 16.5 versus 19.0, P = 0.575, Std diff = 0.0153), prevalence of DM (50% versus 46.4%, P = 0.789, Std diff = 0.0715), need for maintenance dialysis (3.6% versus 3.6%, P = 1.000, Std diff = 0.00), and positive smoking history (28.6% versus 25.0%, P = 0.763, Std diff = 0.0807) between the two groups. Among the 28 matched pairs, the 90-day survival rate of the severe AAC group was significantly lower than that of the non-severe AAC group (53.6% [15/28] versus 82.1% [23/28], P = 0.022; Table 3).

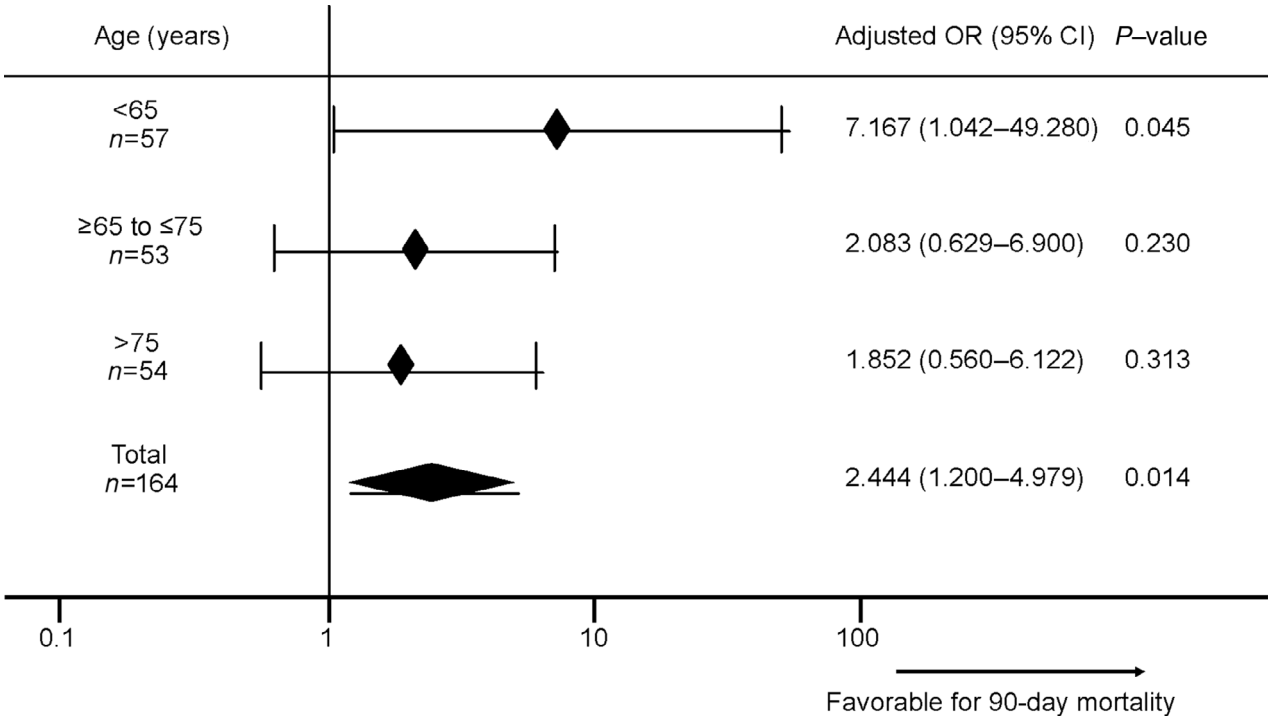

Fig. 2. Subgroup analysis of the association between 90-day mortality and age (<65, 65–75, and >75 years) among sepsis patients admitted to the intensive care unit. Patients with abdominal aortic calcification ratio (AACR) 4 in the group aged <65 years had the highest adjusted odds ratio (OR). CI, confidence interval.

DISCUSSION

THE PROGNOSTIC IMPACT of aortic calcification in sepsis patients is yet to be elucidated. In this study, severe calcification of the abdominal aorta (AACR of 4) was an independent indicator of the SOFA and APACHE II scores and was associated with a significant increase in 90-day mortality in sepsis patients admitted to the ICU. Age-wise subgroup analysis also showed that severe calcification was associated with a significant increase in 90-day mortality in patients aged <65 years. Age, sex, prevalence of DM, hypertension, dyslipidemia, maintenance dialysis, and a

Table 2. Comparison of covariates and 90-day outcomes after matching in sepsis patients admitted to the intensive care unit

	Total (*n* = 56)	AACR = 0–3 (*n* = 28)	AACR = 4 (*n* = 28)	*P*-value	Std diff
Age (years), median (IQR)	74 (68.5–80.00)	74 (68.5–80.75)	75.5 (68.75–79.75)	0.951	0.0018
Sex % (F/M)	30.2 (13 /43)	40.0 (8 /20)	21.7 (5/23)	0.342	0.2558
SOFA score, median (IQR)	9 (7.25–12.75)	9 (7.0–12.0)	9 (8–13.75)	0.592	0.0314
APACHE II score, median (IQR)	18.0 (13.25–25.50)	16.5 (12.5–26.0)	19.0 (13.25–24.0)	0.575	0.0153
Comorbidity (%)					
Diabetes mellitus	27 (48.2)	14 (50.0)	13 (46.4)	0.789	0.0715
Hypertension	40 (71.4)	21 (75.0)	19 (67.9)	0.554	0.1586
Dyslipidemia	14 (25.0)	8 (28.6)	6 (21.4)	0.537	0.1655
Maintenance dialysis	2 (3.6)	1 (3.6)	1 (3.6)	1.000	0.0000
Positive history of smoking	15 (26.8)	8 (28.6)	7 (25.0)	0.763	0.0807

AACR, abdominal aortic calcifications ratio; APACHE, Acute Physiology and Chronic Health Evaluation; F/M, female-to-male ratio; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; Std diff, standardized difference.

Table 3. Ninety-day outcomes in sepsis patients admitted to the intensive care unit after matching

	Total (n = 56)	AACR = 0–3 (n = 28)	AACR = 4 (n = 28)	P-value
Survival rate (%) (dead/alive)	67.9 (18/38)	82.1 (5/23)	53.6 (13/15)	0.022

AACR, abdominal aortic calcification ratio.

positive smoking history were significantly higher in the severe AAC group. This group included older patients, more male participants, and had a significantly higher prevalence of DM, hypertension, dyslipidemia, maintenance dialysis, and a positive smoking history than the other group. The matched-pair cohort analysis to adjust for the confounders showed that severe AAC was associated with a significantly higher 90-day mortality than non-severe calcification, suggesting that it is the calcification, and not the underlying disease causing it, that exacerbates the 90-day mortality.

In this study, severe aortic calcification was observed to affect prognosis, especially in sepsis patients younger than 65 years. Ectopic calcification is a common age-related vascular disease associated with various disease states such as atherothrombotic cardiovascular disease,[8] DM,[4] and CKD.[5] Patients younger than 65 years with severe calcification could have systemic and physical age-related changes as in the elderly; a more careful treatment approach is therefore required, as applied in the latter patient group.

Factors associated with arterial calcification, such as age, blood pressure, DM, maintenance dialysis, CKD, and dyslipidemia, are also associated with a decline in long-term prognosis.[12–16] Sepsis patients often have comorbidities; in the FORECAST study, 67% of sepsis patients had comorbidities.[17] Prognosis is influenced by the presence of comorbidities;[17–19] however, the relationship between an individual factor and prognosis remains controversial. In our study, no single factor significantly impacted the risk for 90-day mortality, consistent with the findings of a previous report.[17] On matched-pair cohort analysis, our results suggested that although severe AAC is specifically associated with poor prognosis in sepsis patients, non-severe calcification is not. Therefore, unlike mild aortic calcification or a comorbidity that promotes vascular calcification, severe calcification could lead to poor prognosis.

Usually, the elastic wall of the aorta acts as an expansive reservoir, transforming pulsatile flow into a more homogeneous flow,[20] but it is known that calcification of the aorta can directly disrupt blood flow in the vasculature[20,21] and reduce aortic compliance.[10] However, De Backer *et al.* reported alterations in the microcirculation of sepsis patients by monitoring the sublingual microcirculation;[22] similar findings have been found in animal models of the stomach, small intestine, colon, liver, and kidney.[23] It has been suggested that tissue reflux could be impaired by altered microvascular flow, thereby reducing the percentage of vessels with adequate flow.[24] In sepsis, advanced aortic calcification could disrupt blood flow and predispose to the development of organ damage by impairing its ability to act as a distensible reservoir for the aorta.

Computed tomography is a convenient and useful technique for determining the risk and extent of aortic calcification. Various studies that use CT and other methods to evaluate aortic calcification[25–27] vary widely with respect to the site, extent, and method of measurement (CT or radiography), and evaluation approach (e.g., large-scale assessments). Examining CT images allowed us to efficiently identify adult patients with potentially poor outcomes, thereby supporting the usefulness of CT in sepsis management, particularly in emergencies.

This study has some limitations. First, there are various confounding factors in clinical practice, such as the indication for admission to the ICU, and the physician's judgment. Although we accounted for several confounding factors to minimize potential bias, some information was unavailable due to the retrospective nature of the study; in addition, the confounding factor of age could be difficult to completely eliminate. Second, the degree of calcification was judged visually, and the results could vary depending on the measurement method's precision. Third, the importance of calcification extent in the cross-section remains unknown. Prospective studies with larger sample sizes are needed to confirm our findings.

In conclusion, severe AAC is associated with poor prognosis in sepsis patients admitted to the ICU, particularly in those aged <65 years. Thus, caution is necessary in sepsis patients with severe aortic calcification who are younger than 65 years; they could require as careful a treatment strategy as that of the elderly.

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DISCLOSURE

Approval of the research protocol: The protocol for this research project was approved by a suitably constituted Committee of Shiga Medical University Hospital (approval No. R2019-197) and it conforms to the provisions of the Declaration of Helsinki.
Informed consent: Informed consent was obtained from all the subjects.
Registry and registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Patient characteristics.
Table S2. Univariate analysis of influencing factors of 90-day mortality (n = 164).
Fig. S1. Evaluation of abdominal aortic calcification ratio (AACR). Reproduced with permission from Elsevier.