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Original Article

Prognostic Value of QRS Duration among Patients with Cardiogenic Shock Complicating Acute Heart Failure: Data from the Korean Acute Heart Failure (KorAHF) Registry

Jung Ae Hong, MD[1], Min-Seok Kim, MD, PhD[1], Hanbit Park, MD[1], Sang Eun Lee, MD[1], Hae-Young Lee, MD[2], Hyun-Jai Cho, MD[2], Jin Oh Choi, MD[3], Eun-Seok Jeon, MD[3], Kyung-Kuk Hwang, MD[4], Shung Chull Chae, MD[5], Sang Hong Baek, MD[6], Seok-Min Kang, MD[7], Dong-Ju Choi, MD[8], Byung-Su Yoo, MD[9], Kye Hun Kim, MD[10], Myeong-Chan Cho, MD[5], Jae-Joong Kim, MD[1], and Byung-Hee Oh, MD[11]

[1]Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[2]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[3]Department of Internal Medicine, Sungkyunkwan University College of Medicine, Seoul, Korea
[4]Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Korea
[5]Department of Internal Medicine, Kyungpook National University College of Medicine, Daegu, Korea
[6]Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea
[7]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[8]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[9]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea
[10]Heart Research Center of Chonnam National University, Gwangju, Korea
[11]Division of Cardiology, Cardiovascular Center, Mediplex Sejong Hospital, Incheon, Korea

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Correspondence to
Min-Seok Kim, MD, PhD
Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
E-mail: msk@amc.seoul.kr

ORCID iDs
Jung Ae Hong
https://orcid.org/0000-0003-3991-7353
Min-Seok Kim
https://orcid.org/0000-0002-8512-797X
Hanbit Park
https://orcid.org/0000-0002-7018-0786
Sang Eun Lee
https://orcid.org/0000-0002-7290-2463
Hae-Young Lee
https://orcid.org/0000-0002-9521-4102
Hyun-Jai Cho
https://orcid.org/0000-0002-2779-4037
Jin Oh Choi
https://orcid.org/0000-0002-2441-2267
Eun-Seok Jeon
https://orcid.org/0000-0002-9946-5611

ABSTRACT

Background and Objectives: Prolonged QRS duration is associated with poor outcomes in patients with chronic heart failure (HF). However, the prognostic value of QRS duration in patients with cardiogenic shock complicating acute HF remains unknown. We evaluated the hypothesis that prolonged QRS duration may be associated with short-term mortality among acute HF patients with cardiogenic shock (CS).
Methods: From March 2011 through December 2013, a total of 5,625 acute HF patients were consecutively enrolled in ten tertiary university hospitals. Among them, we analyzed patients who presented with CS. Patients were divided into three groups by QRS duration cutoff values of 130 and 150 ms. The primary endpoint was 30-day in-hospital mortality.
Results: Two hundred eleven patients presented with CS at admission and those with available electrocardiograms were included in this analysis. There were 35 patients with QRS durations of 150 ms or above, 30 patients with QRS durations between 130 ms and 150 ms, and 146 patients with QRS durations below 130 ms. The 30-day all cause in-hospital mortality rates were 43.7%, 33.1%, and 24.9%, respectively. After multivariate adjustment, severe prolonged QRS duration was a significant prognostic factor for 30-day in-hospital mortality (hazard ratio, 1.909; 95% confidence interval, 1.024–3.558; p=0.042).
Conclusions: Prolonged QRS duration was associated with a higher risk of 30-day in-hospital mortality among patients with acute HF who presented with CS.

Kyung-Kuk Hwang
https://orcid.org/0000-0003-3464-3023
Shung Chull Chae
https://orcid.org/0000-0002-9871-6976
Sang Hong Baek
https://orcid.org/0000-0002-7065-3432
Seok-Min Kang
https://orcid.org/0000-0001-9856-9227
Dong-Ju Choi
https://orcid.org/0000-0003-0146-2189
Byung-Su Yoo
https://orcid.org/0000-0002-3395-4279
Kye Hun Kim
https://orcid.org/0000-0002-6885-1501
Myeong-Chan Cho
https://orcid.org/0000-0002-0047-0227
Jae-Joong Kim
https://orcid.org/0000-0002-2714-2282
Byung-Hee Oh
https://orcid.org/0000-0002-9945-4306

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Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
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Keywords: Heart failure; Cardiogenic shock

INTRODUCTION

Cardiogenic shock (CS) is generally defined as a systolic blood pressure (SBP) <90 mmHg and clinical or laboratory signs of tissue hypoperfusion despite adequate volume status.[1-3] CS has many causes, including acute coronary syndrome (ACS), heart failure (HF), and valvular heart disease, and it is one of the most serious complications of these conditions. Previous studies have shown that in-hospital mortality increases to 40–50% when CS develops in HF patients.[4-7] In this regard, early identification of risk factors associated with CS in HF may prove particularly helpful when considering therapeutic options.

Prolonged QRS duration means electrical and mechanical dyssynchrony in the diseased heart.[8] A wide QRS complex reflecting left-sided intraventricular conduction delay in patients with chronic HF is associated with more advanced myocardial disease, worse left ventricular (LV) function, poorer prognosis, and a higher all-cause mortality rate compared with patients with a narrow QRS complex.[9]

However, the prognostic implications of QRS duration have not been clearly defined in the context of acute HF. The present study aimed to evaluate the prognostic implications of QRS duration and associated factors in a large cohort of acute HF patients with CS. We hypothesized that patients with prolonged QRS duration could represent a high-risk phenotype within the CS spectrum.

METHODS

Study population and data collection

The study population was selected from The Korean Acute Heart Failure (KorAHF) registry, a prospective multicenter cohort study. Patients hospitalized for acute HF from 10 tertiary university hospitals throughout the country were enrolled from March 2011 to February 2014 (NCT01389843). Demographic characteristics, comorbidities, clinical presentation, medical history, laboratory tests, electrocardiographic findings, transthoracic echocardiographic findings, additional treatments, and outcome data were collected at admission and during the follow-up period. Detailed information of the study design and its results have been previously reported.[10][11] Among the patients enrolled in the KorAHF registry, patients who met the following criteria were included in this analysis: 1) patients who were initially diagnosed with CS and 2) were able to undergo baseline electrocardiography. The study protocol was approved by the Ethics Committee/Institutional Review Board (IRB) at each hospital. Written informed consent was obtained from each patient early on during this study; however, the IRBs of each hospital waived the requirement for informed consent, as this study presented minimal risk for the patients and was initiated and sponsored by the Korean Ministry of Health and Welfare to improve public health.

Study design, variables, and statistical analysis

CS was defined as evidence of tissue hypoperfusion induced by HF after adequate correction of preload and major arrhythmia and characterized by reduced SBP (<90 mmHg or a drop

of mean arterial pressure >30 mmHg) and absent or low urine output (<0.5 mL/kg/h).[12] The study sample was classified into three groups based on QRS duration in the baseline electrocardiogram (ECG): 1) patients with QRS durations ≥150 ms (severe prolonged QRS group), 2) patients with QRS durations ≥130 ms and <150 (intermediate prolonged QRS group), and 3) patients with QRS durations <130 ms (narrow QRS group). ECGs were recorded at a standard paper speed of 25 mm/s and calibration of 10 mm/mV. The QRS duration was measured automatically. Complete left bundle branch block (LBBB) and right bundle branch block (RBBB) were identified by standard criteria.[13] The primary endpoint was 30-day in-hospital mortality.

Continuous variables are presented as means±standard deviations and were analyzed by analysis of variance. Categorical variables are represented as percentages and compared using the chi-square test. Mortality analyses were performed using Kaplan–Meier survival curves and Cox proportional hazard ratios (HR). A total of 28 variables, including demographics, clinical presentation, and laboratory and ECG findings, were included in this analysis (**Supplementary Table 1**). The variables with p<0.05 on univariate analysis were included in a multivariate Cox proportional hazard model. HRs are shown with 95% confidence intervals (CIs). The statistical analyses were performed using SPSS Statistics, Version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

Among 5,625 consecutive patients enrolled prospectively in the KorAHF registry, 214 patients who presented with cardiogenic shock at admission were identified. An initial ECG was not available for 3 patients; therefore, 211 patients were included in this analysis. Among these 211 patients, 35 had QRS durations 150 ms or above, 30 had QRS durations between 130 and 150 ms, and 146 had QRS durations below 130 ms (**Figure 1**). The mean age of the 211 patients was 60.6±16.6 years, and 62.6% (n=132) were male. Baseline characteristics were similar between the three groups, except the prevalence of diabetes mellitus (DM). A more prolonged QRS duration was associated with a higher prevalence of DM (**Table 1**).

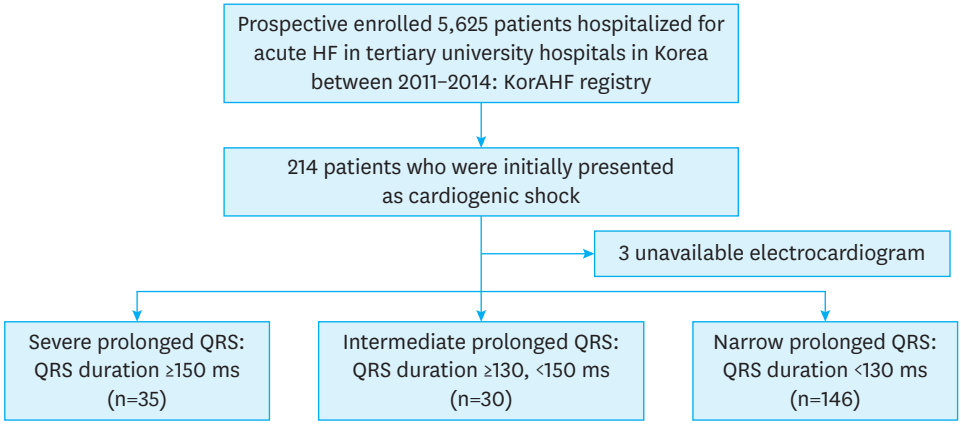

Figure 1. Patient inclusion flow chart.
HF = heart failure; KorAHF = Korean Acute Heart Failure.

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Table 1. Baseline characteristics and laboratory findings

Variables (unit)	Severe prolonged QRS group (n=35)	Intermediate prolonged QRS group (n=30)	Narrow QRS group (n=146)	p value
Age	60.2±15.5	62.7±15.1	60.3±16.6	0.768
Sex (male)	26 (74.3)	18 (60.0)	88 (60.3)	0.302
Body mass index	24.7±4.1	23.6±3.6	23.0±3.6	0.054
SBP	108.6±37.4	96.0±25.6	107.5±31.7	0.242
DBP	68.4±19.2	63.8±20.5	67.2±20.5	0.686
Hypertension	18 (51.4)	14 (46.7)	70 (47.9)	0.933
Diabetes	26 (74.3)	15 (50.0)	65 (44.5)	0.007
Insulin	24 (68.6)	13 (43.3)	60 (41.1)	0.013
Etiology				
Ischemic heart disease	24 (68.6)	21 (70.0)	89 (61.0)	0.533
Valvular heart disease	0 (0.0)	1 (3.3)	7 (4.8)	0.407
Dilated cardiomyopathy	5 (14.3)	2 (6.7)	9 (6.2)	0.259
Stress induced cardiomyopathy	0 (0.0)	0 (0.0)	6 (4.1)	0.253
Chronic lung disease	4 (11.4)	1 (3.3)	12 (8.2)	0.515
Chronic kidney disease	4 (11.4)	1 (1.1)	15 (10.3)	0.478
Stroke	3 (8.6)	3 (10.0)	21 (14.4)	0.601
malignancy	4 (11.4)	3 (10.0)	8 (5.5)	0.410
De novo HF	26 (74.3)	24 (80.0)	109 (74.7)	0.856
Atrial fibrillation	11 (31.4)	10 (33.3)	29 (19.9)	0.138
Medication at admission				
ACEI/ARB	8 (22.9)	5 (16.7)	35 (24.0)	0.685
BB	3 (8.6)	9 (30.0)	34 (23.3)	0.084
MRA	4 (11.4)	4 (13.3)	18 (12.3)	0.973
Labs				
Sodium (mmol/L)	136.8±6.6	137.2±5.9	137.4±5.7	0.882
Hemoglobin (g/dL)	13.3±2.4	12.9±2.5	12.7±2.4	0.368
Potassium (mmol/L)	4.5±1.1	4.3±1.1	4.2±0.8	0.205
Creatinine (mg/dL)	2.38±3.54	1.40±0.71	1.71±2.17	0.199

SBP = systolic blood pressure; DBP = diastolic blood pressure; HF = heart failure; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; MRA = mineralocorticoid receptor antagonist.

Comparison of electrocardiogram and echocardiogram findings among the groups

The overall mean QRS duration was 116.5±33.6 ms. Mean QRS durations differed significantly among the three groups; the values were 175.0±23.0 ms, 138.8±6.5 ms, and 97.8±15.0, in the severe, intermediate, and narrow groups, respectively (**Table 2**). Baseline ECGs revealed ventricular conduction block (VCB) in 28% of the patients (n=55) (**Figure 2**). LBBB was

Table 2. Electrocardiogram and echocardiography findings

Variables (unit)	Severe prolonged QRS group (n=35)	Intermediate prolonged QRS group (n=30)	Narrow QRS group (n=146)	p value
ECG				
QRS duration	175.0±23.0	138.8±6.5	97.8±15.0	<0.001
QTc duration	513.8±52.1	494.1±40.9	458.4±40.0	<0.001
Heart rate (beat/min)	96.1±34.9	99.4±32.9	97.8±29.8	0.914
RBBB	18 (51.4)	11 (36.7)	3 (2.1)	<0.001
LBBB	3 (8.6)	3 (10.0)	0 (0.0)	0.005
Other IVCD	7 (20.0)	10 (33.3)	5 (2.1)	<0.001
Echo				
LVEF (%, n=190)	31.6±14.7	24.9±11.5	33.6±14.8	0.019
LVEDD (mm, n=183)	60.9±14.5	55.5±12.2	53.1±9.0	0.002
LVESD (mm, n=165)	49.2±16.3	45.8±11.0	41.3±11.0	0.007
LA (mm, n=182)	43.2±11.4	41.5±10.9	39.9±8.1	0.215

ECG = electrocardiogram; RBBB = right bundle branch block; LBBB = left bundle branch block; IVCD = intra-ventricular conduction delay; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LA = left atrial diameter.

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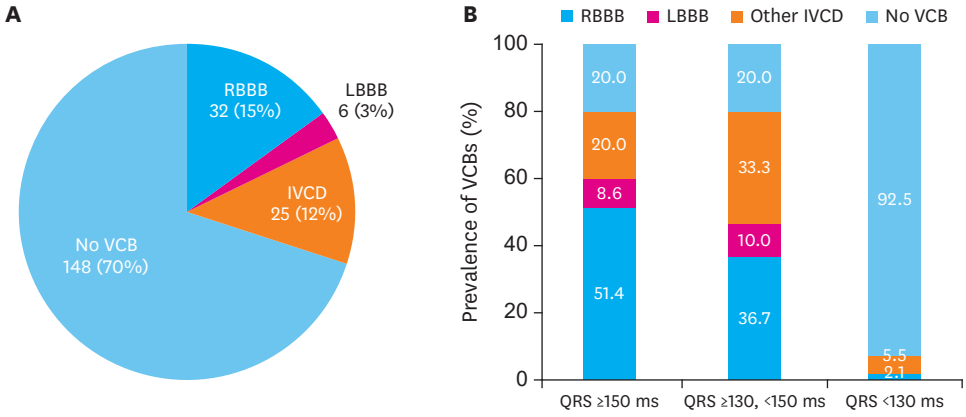

Figure 2. VCBs in the baseline electrocardiogram. (A) Prevalence of VCBs in the entire study sample. (B) Prevalence of VCBs according to QRS duration.
VCB = ventricular conduction block; RBBB = right bundle branch block; LBBB = left bundle branch block; IVCD = intra-ventricular conduction delay.

found in 6 patients and RBBB in 32 patients (**Table 2**). In addition, 25 patients had other intraventricular conduction delays (IVCDs). A more prolonged QRS duration was associated with a higher incidence rate of VCB.

In-hospital course and clinical outcomes

The study sample had a high rate of in-hospital complications and additional management (**Table 3**). Among 211 patients, 59 patients died during hospitalization, 52 of which were classified as cardiac deaths. In-hospital mortality was higher among patients who had longer QRS durations. The 30-day all-cause in-hospital mortality rates were 42.7%, 33.1%, and 24.9%, respectively, in descending order of association with QRS durations (p=0.038). Regarding in-hospital management, patients with longer QRS durations were treated with mechanical circulatory support, including extracorporeal membrane oxygenation (ECMO) and invasive mechanical ventilator support more frequently than patients in the narrow QRS group. However, there were no significant differences among the three groups in terms of renal replacement therapy, intravenous (IV) inotrope, or IV diuretic administration.

In the 30-day all-cause in-hospital mortality analysis, QRS duration was associated with increased short-term mortality risk. The severe prolonged QRS group showed the highest cumulative incidence of 30-day in-hospital death at 42.7%, while the narrow QRS group had

Table 3. In-hospital course and pharmacological treatment

Variables (unit)	Severe prolonged QRS group (n=35)	Intermediate prolonged QRS group (n=30)	Narrow QRS group (n=146)	p value
Death	16 (45.7)	11 (36.7)	32 (21.9)	0.009
Cardiac death	16 (45.7)	10 (33.3)	26 (17.8)	0.001
Heart transplantation	1 (3.8)	3 (13.0)	5 (5.6)	0.425
Hospitalization duration (days)	19.9±16.6	26.8±29.5	23.8±26.0	0.532
ECMO	18 (51.4)	16 (53.3)	45 (30.8)	0.012
Renal replacement therapy	13 (37.1)	9 (30.0)	39 (26.7)	0.480
Mechanical ventilator support	27 (77.1)	24 (80.0)	88 (60.3)	0.035
Support duration (days)	7.8±5.9	7.5±6.3	10.1±22.3	0.737
IV inotrope support*	33 (94.3)	29 (96.7)	126 (86.3)	0.140
IV diuretics	26 (74.3)	24 (80.0)	107 (73.3)	0.784

ECMO = extra corporeal membrane oxygenation; IV = intravenous.
*IV inotrope: dobutamine, dopamine, milrinone, norepinephrine.

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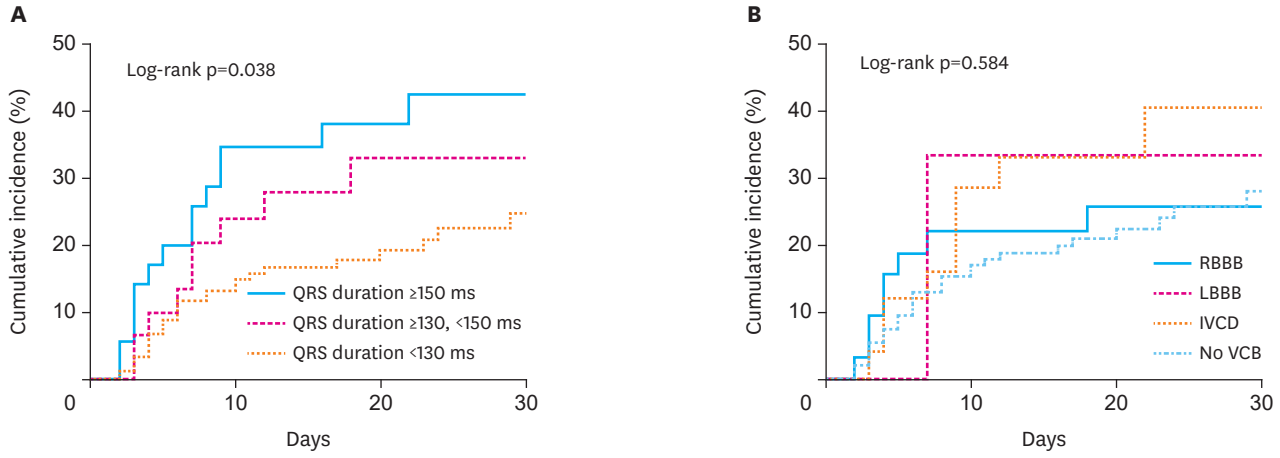

No. at risk				
QRS ≥150 ms	35	24	17	6
QRS ≥130, <150 ms	30	21	13	9
QRS <130 ms	146	100	59	33

No. at risk				
RBBB	32	23	19	9
LBBB	6	6	4	1
IVCD	25	20	11	6
No VCB	148	99	56	32

Figure 3. Cumulative incidence of outcomes according to the QRS duration. (A) The 30-day all cause in-hospital mortality according to QRS duration. (B) The 30-day all cause in-hospital mortality according to ventricular conduction blocks.
RBBB = right bundle branch block; LBBB = left bundle branch block; IVCD = intra-ventricular conduction delay; VCB = ventricular conduction block.

the lowest rate at 24.9% (**Figure 3A**). However, no significant difference was observed in terms of 30-day in-hospital mortality according to the type of ventricular conduction blocks on baseline ECG (**Figure 3B**).

Clinical factors associated with mortality

Clinical factors significantly associated with 30-day in-hospital mortality among HF patients with CS included age, history of ECMO support during admission, hyperkalemia, and severe prolonged QRS duration (QRS ≥150 ms) (**Table 4** and **Supplementary Table 1**). In univariate Cox proportional hazard model, the categorized variable of QRS duration which is divided by the cut-off of 130 ms and 150 ms was statistically significant (the overall p value=0.044). The HR in the severe prolonged QRS group to the narrow QRS group was 2.237 (95% CI, 1.176–4.255; p=0.014), while in the intermediate prolonged QRS group was 1.441 (95% CI, 0.623–3.333; p=0.394). Moreover, this variable divided by cut-off of 130 ms and 150 ms was insignificant as overall p value for 0.114 in multivariate analysis. In multivariate analysis, on the other hand, a binary variable of QRS duration which is divided by the cut-off of 150 ms was an independent factor associated with outcome (HR, 1.909; 95% CI, 1.024–3.558; p= 0.042).

Table 4. Variables associated with 30-day in-hospital mortality

Variables	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.026 (1.007–1.045)	0.007	1.040 (1.020–1.060)	<0.001
Hypertension	1.973 (1.118–3.483)	0.019	1.481 (0.779–2.814)	0.231
Diabetes	1.822 (1.026–3.236)	0.041	1.063 (0.567–1.992)	0.850
Mechanical ventilation	4.594 (1.823–11.579)	0.001	2.118 (0.770–5.824)	0.146
ECMO	3.929 (2.173–7.105)	<0.001	5.370 (2.915–9.891)	<0.001
QRS ≥150 ms	2.042 (1.104–3.779)	0.023	1.909 (1.024–3.558)	0.042
Potassium ≥5.5 mmol/L	3.199 (1.502–6.814)	0.003	3.273 (1.518–7.059)	0.002

HR = hazard ratio; CI = confidence interval; ECMO = extracorporeal membrane oxygenation.

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DISCUSSION

The main conclusions of the present study can be summarized as follows: 1) among patients with wider QRS durations, 30-day in-hospital mortality incidence was higher, while there was no difference in mortality according to the type of ventricular conduction block; 2) age, hyperkalemia, ECMO support during hospitalization, and severe prolonged QRS duration were closely associated with in-hospital mortality.

The majority data associated with CS are so far derived from registries of patients with ACS or myocardial infarction (MI). Of course, the main cause of CS is ACS presenting as MI, but there are other causes, such as HF or valvular heart disease. It is known that CS occurs in about 5–8% of patients with ACS,[14-16] but little is known about CS occurring in the HF setting. A previous EuroHeart Failure Survey II (EHFS II) reported that CS was seen in 3.9% of acute HF cases at presentation.[17] This was similar to our result showing a low incidence of CS (n=214, 3.8%) among 5,625 KorAHF registry patients. The EHFS II registry demonstrated that the in-hospital mortality associated with CS was about 40%. However, the in-hospital mortality from our study was about 28%. This difference may be derived from the increased use of mechanical circulatory support devices (30.9% of IABP use in EHFS II versus 37.4% of ECMO use in KorAHF) or the improvement of intensive care management.

We observed that patients with prolonged QRS duration had a significantly poor prognosis than the narrow QRS group. The longer the QRS duration, the higher the 30-day cumulative mortality incidence in the K–M plot. It is well known that QRS duration is an important prognostic factor for patients with chronic HF.[9][18][19] These studies highlighted QRS duration and morphology because the QRS complex reflects pathologic changes in LV components, such as the conduction system, cardiomyopathy, and ventricular fibrosis.[20][21] However, little is known about the clinical implications of QRS duration in unstable acute HF patients with CS whose ECGs could change dynamically. The study showed that prognosis is affected by a QRS duration that is longer than a certain threshold for a pathologic insult burden on the myocardium.

On the other hand, it is unclear that mechanical dyssynchrony affected clinical outcomes in CS complicating acute HF. Mechanical dyssynchrony was not evaluated here. However, it may not be associated with a poor prognosis. First, QRS duration is known to be inaccurate as a surrogate marker for mechanical dyssynchrnony as a prognostic factor among patients with end-stage HF.[17] Second, the VCB pattern did not have a significant effect on mortality according to the K–M plot and univariate Cox proportional hazard model analysis in the current study; therefore, it meant that QRS duration but not mechanical dyssynchrony reflected by QRS morphology was an independent prognostic factor. Finally, it has been reported that mechanical dyssynchrony by echocardiography tends to be altered according to the loading condition; thus, it is difficult to use a prognostic marker in acute clinical settings.[18]

One study showed that prolonged QRS duration identifies HF in patients with preserved ejection fractions at a higher risk of adverse clinical outcomes independent of QRS morphology.[22] The authors insisted that prolonged QRS duration was solely affected by myocardial fibrosis among many biological parameters. However, the markers of fibrosis could not be assessed using the KorAHF registry data. Besides, a long history of HF may reflect the severity of myocardial fibrosis. However, the numbers of de novo HF cases in the three groups with different QRS durations were similar, with high proportions above 70% (**Table 1**). It is intriguing that myocardial fibrosis may be a prognostic marker in the context of CS associated with acute HF.

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One plausible mechanism by which QRS duration is associated with poor prognosis is an increased LV afterload in cardiogenic shock. The use of vasoconstrictors and compensatory vasoconstriction to maintain blood pressure generally increase myocardial afterload in cardiogenic shock. An abrupt increase in myocardial wall stress is known to widen the QRS complex.[23] In other words, prolonged QRS durations may suggest an excessive increase in LV afterload and poor condition of the patient. The present study showed trends toward higher blood pressure and more use of inotropics in the prolonged QRS duration group, which did not meet statistical significance (**Tables 1** and **2**). Even though this should be further investigated, QRS duration can be used as a prognosticator since it may indicate unstable clinical situation rather than reflect underlying cardiac problem in cardiogenic shock.

Among patients with prolonged QRS durations, the rates of ECMO support and invasive mechanical ventilation support were higher than among patients in the narrow QRS group during hospitalization. These additional supportive interventions reflected the severity of illness. Based on the results of the multivariate Cox proportional hazard model, supporting ECMO during admission was the most significant factor associated with adverse outcomes; mechanical ventilation support was not associated with adverse outcomes. Although ECMO support might indicate the severity of HF itself, it was possible that the complications associated with ECMO itself might have further affected mortality.

First, this was not a randomized controlled trial specifically designed to evaluate the implications of QRS duration as a prognostic factors in acute HF patients with CS. Furthermore, the possibility cannot be ruled out that confounding factors may have influenced the results. However, we believe our analysis is still important as a stimulus for further research. Second, as the study sample was relatively small, the possibility of underestimating the effect of the intermediate prolonged QRS duration and the VCB on 30-day in-hospital mortality could not be excluded.

In conclusion, CS is not an uncommon complication, and it is associated with worse in-hospital short-term mortality. Prolonged QRS duration was associated with a higher risk of 30-day in-hospital mortality among patients with acute HF who presented with CS. Patients with severe prolonged baseline QRS durations should be treated as particularly high-risk patients.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Univariate and multivariate predictors of 30-day in-hospital mortality*

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