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Gender difference in the clinical outcomes of patients with out-of-hospital cardiac arrest

A report using data from a national Korean registry

Gun Tak Lee, MD[a,b], Sung Yeon Hwang, MD[a,b], Ik Joon Jo, MD[a], Tae Rim Kim, MD[a], Hee Yoon, MD[a,b], Won Chul Cha, MD[a], Min Seob Sim, MD[a], Sang Do Shin, MD[c], Tae Gun Shin, MD[a], Jin-Ho Choi, MD[a,*], Cardiac Arrest Pursuit Trial with Unique Registry and Epidemiologic Surveillance investigators

Abstract

We explored gender differences in the characteristics and outcomes of patients with out-of-hospital cardiac arrest (OHCA) in Korea.

We retrospectively analyzed a nationwide multicenter registry of out-of-hospital cardiac arrest patients that prospectively collected from January to December 2014, and explored the clinical outcomes of 670 successfully resuscitated adult patients with OHCA who were transferred to 27 hospitals. The effect of gender on the 30-day neurologically favorable survival (cerebral performance category 1 or 2) was analyzed after propensity score matching (PSM) of each patient in terms of clinical characteristics.

We included 670 patients with OHCA, of whom 482 (72%) were male and 182 (28%) were female. The frequency of witnessed arrests and proportion of home arrests were similar between men and women (73.7% vs 71.3%, $P = .59$, and 55.0% vs 60.6% $P = .21$, respectively). Women were older than men (mean age, 65.9 vs 59.7 years, $P < .001$) and less likely to present with an initial shockable rhythm (27.7% vs 45.0%, $P < .001$). Women were less likely to undergo targeted temperature management (19.1% vs 35.9%, $P < .001$), coronary angiography (14.9% vs 36.1%, $P < .001$), or revascularization (7.4% vs 19.3%, $P < .001$). Compared with men, women exhibited poorer 30-day neurologically favorable survival (69.7% vs 83.0%, $P = .001$). However, the gender difference was not significant on PSM or inverse probability of treatment weighting (IPTW) analyses ($P = .48$ and $P = .63$, respectively).

Female patients with OHCA exhibited poorer clinical characteristics and were less likely to receive treatment than men. After accounting for these differences, clinical outcomes did not differ by gender.

Abbreviations: CABG = coronary artery bypass grafting, CAG = coronary angiography, CAPTURES = Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiological Surveillance, CI = confidence interval, CPC = cerebral performance category, CPR = cardiopulmonary resuscitation, ECMO = extracorporeal membrane oxygenation, ED = emergency department, HR = hazard ratio, IABP = intra-aortic balloon pump, IPTW = inverse probability of treatment weighting, OHCA = out-of-hospital cardiac arrest, PCI = percutaneous coronary intervention, PSM = propensity score matching, ROSC = return of spontaneous circulation, rtPA = recombinant tissue plasminogen activator, SD = standard deviation, TTM = targeted temperature management.

Keywords: cardiac arrest, cardiopulmonary resuscitation, gender, prognostication, survival

Editor: Abdelouahab Bellou.

TGS and JHC contributed equally to this work.

This study was financially supported by the Korea Centers for Disease Control and Prevention (2013–2014; grant nos. 2013E3300500/2014E3300100). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Drs Jin-Ho Choi, Won Chul Cha, and Sang Do Shin were the Cardiac Arrest Pursuit Trial Unique Registry and Epidemiologic Surveillance investigators in this study.

The study protocol was approved by all Institutional Review Boards of 27 participating hospitals with waiver of informed consent.

The institutional review board of Samsung Medical Center approved this study. (IRB file number: 2018-08-181) Informed consent was waived because this study was of a retrospective, observational, and anonymous nature.

The authors declare no conflict of interest.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

[a] Department of Emergency Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [b] Department of Emergency Medicine, College of Medicine, Kangwon National University, Chuncheon, Gangwon, Korea, [c] Department of Emergency Medicine, Seoul National University College of Medicine, Seoul, Korea.

[*] Correspondence: Jin-ho Choi, Department of Emergency Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea (e-mail: jhchoimd@gmail.com).

How to cite this article: Lee GT, Hwang SY, Jo IJ, Kim TR, Yoon H, Cha WC, Sim MS, Shin SD, Shin TG, Choi JH, Cardiac Arrest Pursuit Trial with Unique Registry and Epidemiologic Surveillance investigators. Gender difference in the clinical outcomes of patients with out-of-hospital cardiac arrest: a report using data from a national Korean registry. Medicine 2021;100:48(e27855).

Received: 11 June 2020 / Received in final form: 24 September 2020 / Accepted: 1 November 2021

http://dx.doi.org/10.1097/MD.0000000000027855

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health problem associated with high morbidity and mortality.[1–3] The worldwide prevalence of cardiac arrest ranges from 45 to 110 per 100,000 of the population.[4–6] Survival after OHCA is extremely poor; 90% of patients die.[1,2,5,7,8] Several studies have explored OHCA outcomes by gender, but the data are inconsistent.[4,9–22] In most studies, the proportions of men were higher than that of women; witnessed arrest and shockable rhythm were more frequent in men; and women were older than men.[9,10,19,21,22] The observational study of Karlsson et al found that survival and neurological outcomes of men were better; after adjusting for confounding variables, no significant difference in neurological outcome was evident, but survival in men remained better.[9] In another study using a nationwide registry, the subgroup analysis by initial rhythm showed that the 30-day survival rate was better in women than in men when the initial rhythm was shockable.[22] In addition, several studies have reported higher long-term survival rates in relatively young women than in men.[16,17,23,24] However, the Australian study of Bray et al found that, regardless of the initial rhythm, survival to the time of hospital arrival was higher in women than in men, but there was no significant difference in terms of survival to discharge.[10] Thus, previous results are not in complete agreement.

Here, we explored gender-specific differences in patients with OHCA using data from a national, multicenter Korean OHCA registry. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) analyses were used to minimize indication bias.

2. Materials and methods

2.1. Data collection and study population

The Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance (CAPTURES) project was a Korean multicenter observational study conducted from January to December 2014 in 27 emergency departments (EDs) (level 1, n = 9; level 2, n = 18). The project aimed to identify risk factors for OHCA and evaluate prognostic factors evident in a long-term follow-up. The CAPTURES project included patients transported to participating EDs after resuscitation efforts had been made in the ambulance; all had a presumed cardiac etiology, as identified by emergency physicians in the EDs.

Patients with OHCA with definite non-cardiac etiologies, such as trauma, drowning, hanging, poisoning, asphyxia, burning, or hemorrhagic or ischemic stroke, aged < 18 years, and with terminal illnesses were excluded. Data collected by all EDs were transferred to a central server using the EpiData software (version 3.1; The EpiData Association, Odense, Denmark). Our previous studies on prognosis by coronary angiography (CAG) status used the same data.[25,26]

2.2. Clinical variables and outcome measurements

We extracted data on general patient characteristics, that is, age, gender, comorbidities (including chronic hypertension, diabetes mellitus, and dyslipidemia), and prehospital arrest data, including arrest location (in a public place, at home, or in a healthcare facility), bystander witness status, bystander cardiopulmonary resuscitation (CPR), prehospital defibrillation, ED arrival during business hours, and first documented cardiac rhythm (non-shockable or shockable). In-hospital data included intubation status; use of intravenous inotropic agents; CAG; revascularization, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting; use of recombinant tissue plasminogen activator; mechanical circulatory support, including an intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO); and targeted temperature management (TTM).

The primary outcome was death within 30 days or an unfavorable neurological outcome at discharge, as revealed by the Glasgow-Pittsburgh cerebral performance category (CPC) score. A good outcome was survival with a favorable neurological outcome (CPC score of 1 or 2), and a poor outcome was defined as a CPC score of 3 to 5 or all-cause death within 30 days.

2.3. Statistical analysis

Standard descriptive statistics are presented for all variables. The results are shown as means ± standard deviation (SD) for continuous variables and numbers of patients with percentages for categorical data. Data were compared using the Mann–Whitney *U* test or chi-squared test, as appropriate. A Cox's proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the clinical outcomes of the groups. Comparisons were adjusted via PSM and IPTW to reduce indication bias. In PSM analysis, 1:1 matched pairs were selected based on the predicted probability of being male or female. We developed a non-parsimonious model including clinical characteristics; age; gender; chronic hypertension, diabetes, and dyslipidemia status; location of arrest; bystander witness and resuscitation; initial rhythm; prehospital defibrillation; ED arrival during business hours; intubation status; use of intravenous inotropic agents; revascularization status; and application of ECMO, IABP, and TTM.

The population was divided into 5 quintiles by their propensity scores. The mean propensity scores of men and women were compared within each quintile. The Hosmer–Lemeshow tests for goodness-of-fit were applied, and *c*-statistics was evaluated to confirm that calibration and discrimination were satisfactory. The propensity score distributions in the PSM and IPTW analyses are shown in Fig. 1. Statistical significance was denoted by a 2-tailed *P*-value <.1. R software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria) was used in all analyses.

3. Results

3.1. Baseline characteristics

During the study period, a total of 1616 patients with OHCA were registered by the CAPTURES project. Of these, 946 were excluded because of a lack of return of spontaneous circulation (ROSC; n = 854), absence of transfer by an emergency medical service or lack of documentation (n = 66), age <18 years (n = 19), and an initial sinus rhythm (n = 7). A total of 670 patients with OHCA were included in the final analysis, of whom 488 were male and 188 were female. Their baseline characteristics are summarized in Table 1.

The overall poor outcome rate was 73.4% (n = 492). Overall, the proportion of witnessed arrests was 73.0% (n = 489), and the bystander CPR rate was 47.3% (n = 317). At the prehospital stage, 40.1% (n = 269) of the initial rhythms were shockable; defibrillation was performed in 42.4% of patients (n = 284), and

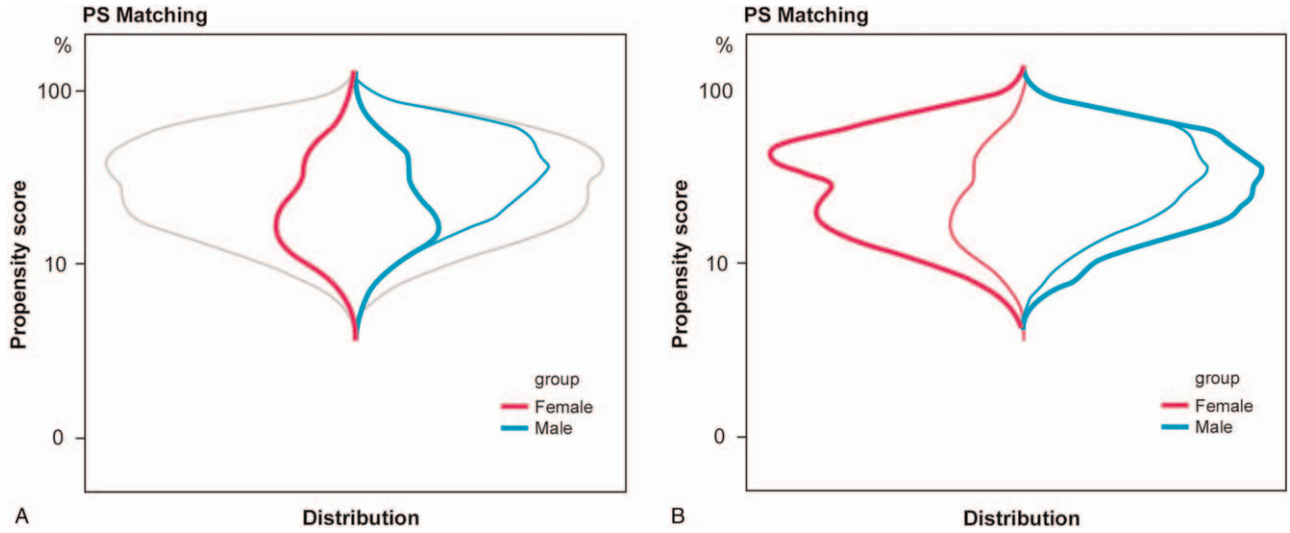

Figure 1. PSM and IPTW analyses of adult patients with OHCA by gender. IPTW = inverse probability of treatment weighting, OHCA = out-of-hospital cardiac arrest, PSM = propensity score matching.

most cardiac arrests occurred at home or in unknown locations (56.6%; n = 379). Revascularization was performed in 16.0% of patients (n = 107).

Compared with men, women were older (mean age, 65.9 vs 59.7 years, $P < .001$) and more likely to have a history of chronic hypertension (46.8% vs 36.5%, $P = .018$) and had a lower frequency of shockable rhythm (27.7% vs 45.0%, $P < .001$) and lower rate of prehospital defibrillation (28.2% vs 47.9%, $P < .001$). In addition, fewer CAG (14.9% vs 36.1%, $P < .001$), PCI (3.7% vs 13.9%, $P < .001$), and TTM (19.1% vs 35.9%, $P < .001$) procedures were performed, and more women died or exhibited poor CPC scores at discharge (83.0% vs 69.7%,

Table 1

Baseline characteristics of the patients with out-of-hospital cardiac arrest.

Characteristics	All (N = 670)	Men (n = 482)	Women (n = 188)	*P*
Age[§]	61.4 (±15.9)	59.7 (±14.7)	65.9 (±18.1)	<.001
Preexisting conditions – n (%)				
Hypertension	264 (39.4)	176 (36.5)	88 (46.8)	.018
Diabetes	144 (21.5)	105 (21.8)	39 (20.7)	.85
Dyslipidemia	41 (6.1)	29 (6.0)	12 (6.4)	1
Bystander witnessed – n (%)	489 (73.0)	355 (73.7)	134 (71.3)	.59
Bystander CPR – n (%)	317 (47.3)	235 (48.8)	82 (43.6)	.26
Initial shockable rhythm – n (%)	269 (40.1)	217 (45.0)	52 (27.7)	<.001
Prehospital defibrillation – n (%)	284 (42.4)	231 (47.9)	53 (28.2)	<.001
Arrest location[*] – n (%)	379 (56.6)	265 (55.0)	114 (60.6)	.21
ED visit not during working hours[†] – n (%)	179 (26.7)	231 (47.9)	98 (52.1)	.37
Hospital course – n (%)				
Intubation	618 (92.2)	442 (91.7)	176 (93.6)	.50
Use of inotropic agents	496 (74.0)	348 (72.2)	148 (78.7)	.10
CAG	202 (30.1)	174 (36.1)	28 (14.9)	<.001
Revascularization – n (%)	107 (16.0)	93 (19.3)	14 (7.4)	<.001
PCI	74 (11.0)	67 (13.9)	7 (3.7)	<.001
CABG	8 (1.2)	7 (1.5)	1 (0.5)	.55
rTPA	39 (5.8)	30 (6.2)	9 (4.8)	.59
IABP	22 (3.3)	20 (4.1)	2 (1.1)	.07
ECMO	32 (4.8)	27 (5.6)	5 (2.7)	.16
TTM	209 (31.2)	173 (35.9)	36 (19.1)	<.001
Poor outcome[‡] – n (%)	492 (73.4)	336 (69.7)	156 (83.0)	.001

CABG = coronary artery bypass grafting, CAG = coronary angiography, CPC = cerebral performance category, CPR = cardiopulmonary resuscitation, ECMO = extracorporeal membrane oxygenation, IABP = intra-aortic balloon pump, PCI = percutaneous coronary intervention, rtPA = recombinant tissue plasminogen activator, SD = standard deviation, TTM = targeted temperature management.

[*] Arrest occurring in a private home or unknown location.

[†] 5 p.m. to 8 a.m. and weekends.

[‡] Defined as CPC ranging from 3 to 5 or all-cause death within 30 days.

[§] Values are means ± SD.

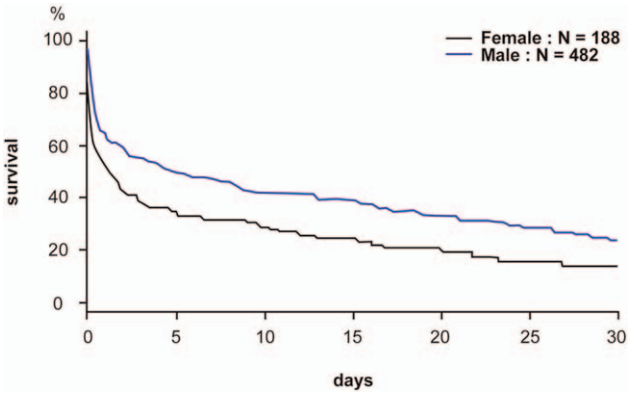

Figure 2. Unadjusted 30-day survival curve for adult patients with OHCA*. CPC = cerebral performance category, OHCA = out-of-hospital cardiac arrest. *Death or poor neurological outcome (CPC score 3–5) despite survival.

$P = .001$). However, there was no statistically significant gender difference in the rate of witnessed arrest, arrest location, intubation status, or use of inotropic agents.

3.2. Clinical outcomes by gender

On crude analysis of overall outcomes before PSM and IPTW adjustment, men had a lower risk of death or poor CPC score than women (HR, 0.67; 95% CI, 0.56–0.82; $P < .001$). The Kaplan–Meier survival curve for the unadjusted model is shown in Fig. 2.

After PSM or IPTW adjustment, 30-day survival with a favorable neurological outcome did not significantly differ between men and women. The Kaplan–Meier survival curves of the PSM and IPTW models are shown in Fig. 3.

4. Discussion

OHCA is a major problem associated with high mortality and morbidity; a good understanding of the clinical characteristics of such patients is essential to improve prognosis. Here, we accessed a nationwide, multicenter OHCA registry to explore the prognostic significance of gender. A crude analysis showed that men had better clinical outcomes than women, but no difference was apparent in PSM or IPTW analyses.

In our study, women were older and more frequently had initial non-shockable rhythm; therefore, prehospital defibrillation was less common in women, which is similar to that reported in previous studies. In contrast, there were no gender differences in witnessed arrest, bystander CPR, and location of cardiac arrest. This result differed from previous studies in which men had more witnessed arrest and bystander CPR than women.[9,10,15,21] The differences may be attributable to differences in the inclusion criteria (e.g., inclusion only of patients exhibiting ROSC and inclusion of those with all-cause cardiac arrest or only cardiac arrest of cardiac etiology). Moreover, the endemic features of studies may vary. Here, in additional analyses including patients who did not have ROSC, a statistically significant difference in the witnessed arrest rate was found by gender (men vs women, 61.8% vs 56.4%, $P = .039$), but the rates of bystander CPR were similar (men vs women, 43.4% vs 43.5%, $P = .97$).

Moreover, in this study, women tended to have fewer resuscitation efforts, such as TTM (men vs women, 35.9% vs 19.1%, $P < .001$), ECMO (men vs women, 5.6% vs 2.7%, $P = .16$), and revascularization (men vs women, 19.3% vs 7.4%, $P < .001$), than men. Coronary artery disease is one of the most common causes of adult OHCA, and previous studies have shown that the prognosis was different between genders.[5,27–29] One previous study concluded that this difference was due to health behavior, psychological distress, and metabolic dysregulation.[28] Jneid et al reported that women had fewer early aspirin and beta-blocker treatments and fewer timely reperfusion therapies than men. In addition, women were found to have fewer cardiac catheterizations and revascularizations after acute myocardial infarction.[29] In our study, location of cardiac arrest, witnessed arrest, and presence of bystander CPR were not significantly different between genders; nevertheless, the resuscitation effort was significantly less in women, which is similar to that observed in previous studies. Resuscitation effort seems to be more conservative in women.

In terms of the primary study outcome (survival with good neurological outcomes; CPC score of 1 or 2), crude analysis showed that men had better clinical outcomes than women, but no significant difference was apparent on PSM or IPTW analyses. Thus, the difference in clinical outcomes evident in the unadjusted

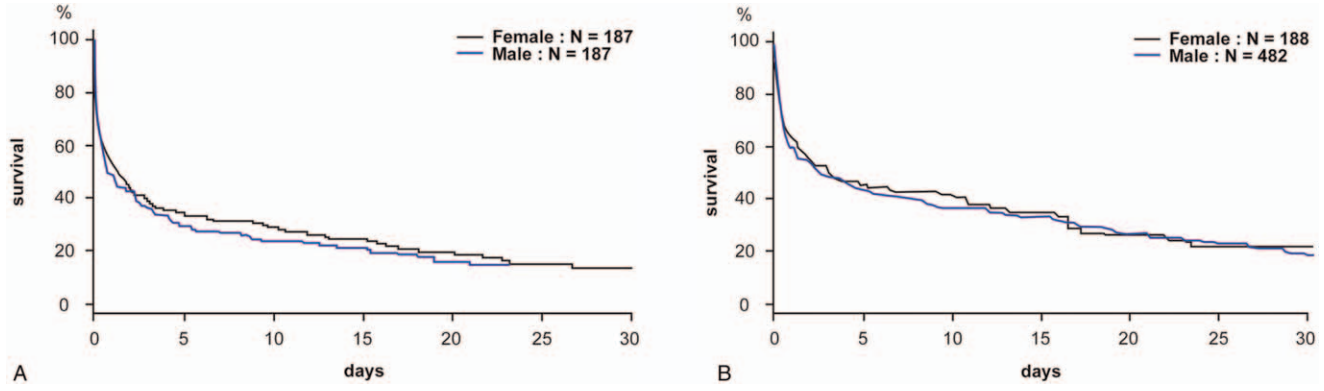

Figure 3. PSM (left)* and IPTW (right) † analysis of adult patients with OHCA by gender‡. CPC = cerebral performance category, IPTW = inverse probability of treatment weighting, OHCA = out-of-hospital cardiac arrest, PSM = propensity score matching. *Log-rank test $P = .48$ for PSM. †Log-rank test $P = .63$ for IPTW. ‡Death or poor neurological outcome (CPC score 3–5) despite survival.

model was attributable principally to differences in clinical characteristics directly related to the outcome, such as frequency of initial shockable rhythm (which is more favorable than a non-shockable rhythm), proportion of prehospital defibrillation, and frequency of chronic hypertension, rather than to a gender difference. Previous studies on OHCA prognosis by gender were inconsistent because of such effects.[9,16,17,20,21] Thus, any effect of gender on the prognosis of patients with OHCA with cardiac etiologies is negligible.

In a study by Herlitz et al,[13] among cardiac arrest victims, men were more likely to have an underlying cardiac etiology than women. In another study by Wissenberg et al,[21] women presented more often with a medical history of chronic obstructive pulmonary disease, malignancy, or psychiatric illness, whereas men presented more with cardiovascular disease and diabetes. Because of these differences in characteristics between men and women, the causes of cardiac arrest may not be the same, and indeed, in a study by Karlsson et al,[9] cardiac causes and ST elevation myocardial infarction (STEMI) were more frequent in men as causes of arrest than in women. Because detailed causes of cardiac arrest were not obtained in the registry, the effect of gender on the clinical outcome of cardiac arrest may have been underestimated. However, patients with definite extracardiac etiology were excluded from this study, and interventions, including CAG, revascularization, and TTM, were adjusted to ensure that the etiology-related bias is small.

Our study had certain limitations. First, although we used a nationwide multi-institutional registry, the size of the study population was relatively small. Second, PSM and IPTW analyses may not adequately consider functional status, comorbidities, or familial/social factors. Third, patients with OHCA with definitive non-cardiac etiologies were excluded, as were patients who did not exhibit ROSC. Thus, it is difficult to generalize our results to all patients with OHCA. Further studies on patients with various clinical characteristics are required.

5. Conclusion

In this nationwide, multicenter study of OHCA in Korea, gender did not affect the probability of survival; some adult patients with OHCA had good neurological outcomes. The clinical outcomes seemed to be determined by the initial rhythm (shockable vs non-shockable), comorbidities, whether cardiac arrest was witnessed, and whether defibrillation and revascularization were performed; no gender difference was apparent. However, further studies are needed to confirm our findings in different settings.

Author contributions

Conceptualization: Gun Tak Lee, Jin-Ho Choi.
Data curation: Sung Yeon Hwang, Ik Joon Jo, Won Chul Cha, Sang Do Shin.
Funding acquisition: Sang Do Shin.
Investigation: Hee Yoon, Won Chul Cha.
Methodology: Hee Yoon, Min Seob Sim.
Software: Ik Joon Jo, Tae Rim Kim.
Supervision: Tae Gun Shin, Jin-Ho Choi.
Validation: Sung Yeon Hwang, Min Seob Sim, Tae Gun Shin.
Writing – original draft: Gun Tak Lee.
Writing – review & editing: Tae Gun Shin, Jin-Ho Choi.

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