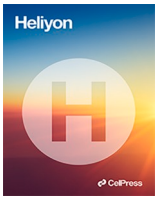
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Research article



Seasonal variation and prognosis in patients with acute myocardial infarction complicated by cardiogenic shock

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ABSTRACT

Background: Little is known about the association between seasonal variation and prognosis in patients with CS caused by AMI.
Objectives: We investigated the 12-month clinical outcomes in patients treated with percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) according to season.
Methods: A total of 695 patients undergoing PCI for AMI complicated by CS was enrolled from 12 centers in South Korea. The study patients were divided into four groups according to season in which the AMI with CS occurred (spring, n = 178 vs. summer, n = 155 vs. autumn, n = 182 vs. winter, n = 180). We compared major adverse cardiovascular events (MACEs; the composite of cardiac death, myocardial infarction, re-hospitalization due to heart failure, and any revascularization) between the four groups.
Results: The risk of MACE during the 12 months after CS was similar in the four groups: spring, 68 patients, vs. summer, 69, vs. autumn, 73, vs. winter, 68 ($p = 0.587$). Multivariate Cox-regression analysis revealed no significant difference in 12-month MACE among groups compared to the spring group after inverse probability of treatment weighting adjustment (summer, HR 1.40, 95 % CI 0.98–1.99, $p = 0.062$; autumn, HR 1.26, 95 % CI 0.89–1.80, $p = 0.193$; winter, HR 1.18, 95 %

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CI 0.83–1.67, $p = 0.356$). The similarity of MACE between the four groups was consistent across a variety of subgroups.
Conclusions: After adjusting for baseline differences, seasonal variation seems not to influence the mid-term risk of 12-month MACE in patients treated with PCI for AMI complicated by CS.
Condensed abstract: Data are limited regarding the association between seasonal variation and prognosis in patients with cardiogenic shock (CS) caused by AMI. This study divided patients undergoing PCI for AMI complicated by CS into four groups based on the season of occurrence and found no significant differences in 12-month MACE between the groups after adjusting for bias and confounding factors. Multivariate analysis revealed consistent MACE similarity across subgroups. The study suggests that seasonal variation has no impact on the mid-term risk of 12-month MACE in patients with CS caused by AMI, after adjusting for baseline differences.
Trial registration: ClinicalTrials.gov NCT02985008RESCUE (REtrospective and prospective observational Study to investigate Clinical oUtcomes and Efficacy of left ventricular assist device for Korean patients with cardiogenic shock), NCT02985008, Registered December 5, 2016 - retrospectively and prospectively.
Irb information: This study was approved by the institutional review board of Samsung Medical Center (Reference number: 2016-03-130).

Abbreviations

AMI = acute myocardial infarction
CS = cardiogenic shock
IPTW = inverse probability of treatment weighting
MCS = mechanical circulatory support
MACE = major adverse cardiovascular event
PCI = percutaneous coronary intervention
SCAI = society for cardiovascular angiography & interventions
STEMI = ST-segment elevation myocardial infarction
TIMI = thrombolysis in myocardial infarction

1. Introduction

Extreme or changed temperatures were associated with increased incidence and mortality of acute myocardial infarction (AMI) [1–3]. Actually, AMI frequently occurs in the winter with cold and dry climates [4,5] or in the summer with hot and humid weather [6,7] in countries with four seasons. Kloner RA et al. reported that seasonal variations affect myocardial perfusion, investigated through the measurement of myocardial infarct size by the cumulative release of cardiac enzymes, and showed smaller infarct size in the summer. enzymatic infarct size by the cumulative release of cardiac enzymes, and showed smaller infarct size in the summer [8]. These findings were supported by evidence of various mechanisms, such as potential effects of temperature on blood viscosity, vascular resistance, and platelet activation [4,9]. Moreover, some studies reported seasonal variations in the development of coronary morbidity and mortality, which occur more in colder temperatures [10,11]. AMI is complicated by cardiogenic shock (CS) frequently, and it is a serious and potentially life-threatening condition that requires urgent intervention [12]. However, previous studies about AMI mostly excluded patients complicated with CS, and there are limited data on clinical outcomes about CS caused by AMI; therefore, prognoses according to seasonal changes have rarely been reported in patients with AMI complicated by CS [13,14]. In the present study, we evaluated the 12-month clinical outcomes according to the season in which the AMI occurred in patients treated with percutaneous coronary intervention (PCI) for AMI complicated by CS.

2. Methods

2.1. Study population

Study subjects were recruited from the REtrospective and prospective observational Study to investigate Clinical oUtcomes and Efficacy of left ventricular assist device for Korean patients with cardiogenic shock (RESCUE) registry, which is a multicenter, retrospective, and prospective database of patients with CS [15]. Between January 2014 and December 2018, a total of 1247 CS patients was recruited from 12 tertiary centers in South Korea. The inclusion criteria were as follows [1]: older than 19 years [2], systolic blood pressure less than 90 mmHg for 30 min or need for inotrope or vasopressor support to achieve a systolic blood pressure greater than 90 mmHg, and [3] presence of pulmonary congestion and signs of impaired organ perfusion (altered mental status, cold peripherals, urine output under 0.5 mL/kg/h for the previous 6 h, or blood lactate over 2.0 mmol/L). Exclusion criteria were [1]

patients with out-of-hospital cardiac arrest [2], other causes of shock, and [3] those who refused active treatment. For this study, 695 cases of CS caused by AMI for which the patient underwent PCI were selected. Patients for whom coronary angiography (CAG) was not performed (n = 26), who did not receive revascularization or failed culprit lesion PCI (n = 28), who went through coronary artery bypass grafting (CABG; n = 42), and who showed vasospasm (n = 7) were excluded. For this study, we categorized patients into four groups based on the season when acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) occurred. The cohort selection process outlined above is visually represented in Fig. 1.

2.2. Data collection

Independent clinical research coordinators collected patient demographics, in-hospital management, laboratory data, procedural data, and outcome data using web-based case report forms. All baseline data were measured upon admission. Additional information was obtained from medical records or telephone contact, if necessary.

2.3. Ethics statement

This study was approved by the institutional review board (IRB) of Samsung Medical Center (Reference number: 2016-03-130). IRB approval was obtained at each participating site, and the IRB of each participating center waived the requirement for informed consent in retrospectively enrolled patients. Informed consent was obtained before enrollment in all prospectively enrolled patients.

2.4. Season and definition of study group

Korea has a temperate climate with four distinct seasons, where the annual mean temperature ranges from 10 to 16 °C, and the extremes range from −32.6 to 40.0 °C, according to the Korea Meteorological Administration [16]. The four seasons are spring (March to May), summer (June to August), autumn (September to November), and winter (December to February). The summers have high temperatures and humidity, while the winters are cold and dry, and the spring and autumn months generally are relatively mild. In this study, patients were divided into four groups according to season of AMI complicated by CS.

2.5. PCI and pharmacologic therapy

PCI was performed in accordance with standard techniques [17]. Unfractionated heparin or low-molecular-weight heparin was

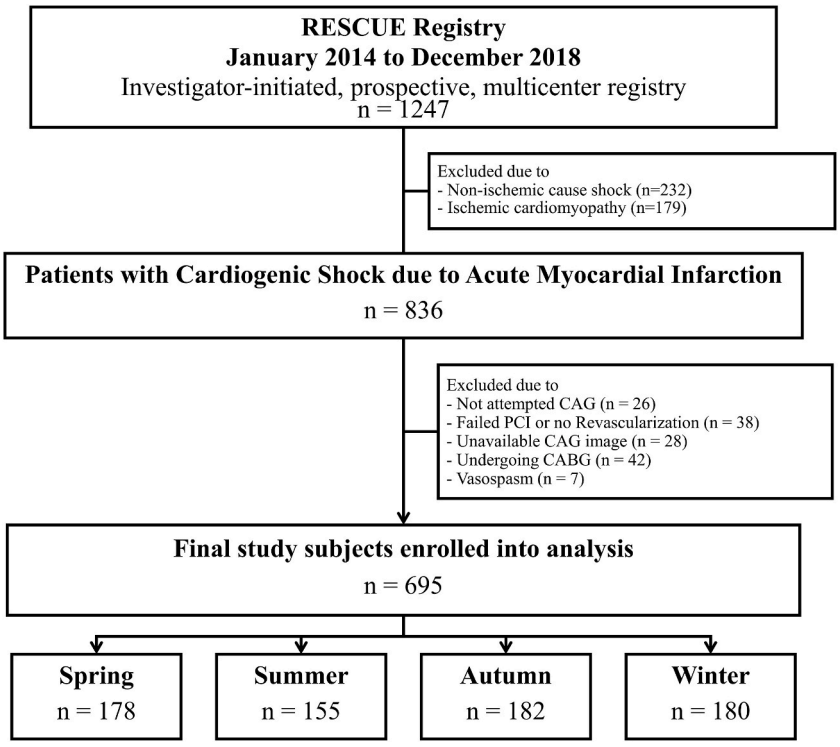


Fig. 1. Schematic illustration of study cohort selection CABG = coronary artery bypass grafting; CAG = coronary angiography; PCI = percutaneous coronary intervention.

used for anticoagulation during the procedure. The decision to perform thrombus aspiration, pre-dilation or post-dilation, or to use glycoprotein IIb/IIIa inhibitors was determined by the operator. The use of intravascular imaging or fractional flow reserve was also performed at the operator's discretion. The length and diameter of stents used for PCI varied. All patients who were not taking aspirin or a P2Y12 inhibitor were administered a loading dose of aspirin (300 mg) or P2Y12 inhibitor (clopidogrel 600 mg, ticagrelor 180 mg, or prasugrel 60 mg). After the procedure, aspirin (100 mg orally once daily) was maintained indefinitely; clopidogrel (75 mg orally once daily), ticagrelor (90 mg orally twice daily), or prasugrel (10 mg orally once daily) was continued. Anticoagulation during PCI was performed using low-molecular-weight heparin or unfractionated heparin to achieve an activated clotting time of 250–300 s. All patients were recommended to receive optimal pharmacological therapy, including statins, beta-blockers, or renin-angiotensin system blockade if indicated, and the responsible clinicians determined the duration of dual antiplatelet therapy [18,19].

2.6. Study outcomes and definitions

The primary outcome of this study was major adverse cardiovascular events (MACEs), defined as a composite of cardiac death, myocardial infarction, re-hospitalization due to heart failure, and repeat revascularization. Secondary outcomes were consistent with the individual components of the primary outcome, as well as all-cause death. Clinical events were defined based on recommendations from the Academic Research Consortium [20]. Analyses were truncated at 12 months of follow-up due to the different follow-up durations.

2.7. Statistical analysis

Categorical variables are presented as count and percentage, and differences were compared using the χ^2 test or Fisher's exact test. Continuous variables are presented as mean ± standard deviation or as median (25th percentile to 75th percentile) for variables lacking a normal distribution. Continuous variables with dichotomous factor variables were analyzed using Student's t-test or One-way ANOVA, and continuous variables with multinomial factor variables were analyzed by Wilcoxon rank-sum test or Kruskal-Wallis test based on normality. Kaplan–Meier estimates were used to generate survival curves and compared with the log-rank test. Cox proportional hazard models were used to demonstrate hazard ratio (HR) and 95 % confidence interval (CI), and to compare the outcomes of the groups. The proportional hazards assumptions of the HRs were graphically inspected in the "log minus log" plot in the Cox proportional hazards models and were tested by Schoenfeld residuals. Inverse probability of treatment weighting (IPTW) analysis was performed to reduce selection bias and to control confounding factors (age, sex, hypertension, diabetes mellitus, current smoking, serum creatinine, and left ventricular ejection fraction). The covariate balance after IPTW adjustment was assessed as absolute standardized mean difference. Standardized mean differences after IPTW adjustment were within ±10 % across all matched covariates with variance ratios near 1.0, suggesting balance between among the four season groups. Stratified Cox proportional hazard models were used to compare the outcomes of the matched groups. All probability values were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using R Statistical Software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline clinical characteristics

Among the 695 patients enrolled in this study, CS was observed in 25.6 % of patients in the spring group (n = 178), 22.3 % in the summer group (n = 155), 26.2 % in the autumn group (n = 182), and 25.9 % in the winter group (n = 180) with no significant difference (Fig. 1). Baseline clinical characteristics of age, sex, body mass index (BMI), and underlying cardiovascular risk factors did not differ significantly between the four season groups. CKD was more prevalent among patients presenting in the spring season compared to other seasons, with an incidence of 11.8 % versus an average of 7.2 %, respectively. Similarly, the incidence of previous MI was higher in patients presenting in the spring season (16.9 %) compared to other seasons (average 11.1 %). However, these differences did not reach statistical significance in the analysis.

NSTEMI and STEMI occurred in 202 (29.1 %) and 493 (70.9 %) patients, respectively, and the difference was not statistically significant ($p = 0.085$). Mean heart rate and systolic and diastolic pressure were 78.6 ± 32.7, 74.6 ± 29.5, and 47.5 ± 20.0, respectively. Baseline hemoglobin, creatinine, glucose, and lactate levels, which reflect the severity of the clinical condition, were also similar between the four groups. Peak Troponin I levels were elevated among patients presenting in the autumn season (mean 111.2 ± 225.3 ng/mL) compared to other seasons (mean 77.6 ± 137.9 ng/mL). The involvement of the left circumflex artery (LCX) as the culprit lesion was less common among patients presenting in the autumn season (2.2 %) compared to other seasons (average 5.2 %).

The Society for Cardiovascular Angiography and Intervention (SCAI) shock classification, when applied to the study population, resulted in 328 (47.2 %) patients in stage C or D and 367 (52.8 %) in stage E ($p = 0.523$), and the number of patients undergoing cardiopulmonary resuscitation was 148 (21.3 %), with even proportions across the four season groups. The vasoactive inotropic score, which objectively quantifies the degree of hemodynamic support, was 80.0 ± 155.4, and the IABP-SHOCK 2 score, which predicts 30-day all-cause mortality, was 2.2 ± 1.7; and these scores were consistent across all groups. Mechanical ventilation, requirement for renal replacement therapy, intra-aortic balloon pump, and extracorporeal membrane oxygenator use showed no statistical differences between the groups (Table 1). Angiographic and procedural characteristics showed no significant differences in angiographic findings, including culprit lesion location, pre- and post-thrombolysis in myocardial infarction (TIMI) flow at the culprit lesion, number of

diseased vessels or lesions, access site (femoral artery: 573 [82.4 %]), or treatment strategy. Second-generation drug-coated stents were used in 631 (90.9 %) cases, and 54 (7.8 %) patients received only balloon angioplasty or thrombectomy. The mean number of stents used was 1.3 ± 0.8, and thrombus aspiration and glycoprotein IIb/IIIa inhibitors were used in 235 (33.8 %) and 137 (19.7 %) cases, respectively. In 536 (77.1 %) cases with multi-vessel disease undergoing PCI, 369 received culprit-only PCI, which represents 53.1 % of overall PCI and 68.8 % of multi-vessel disease PCI (Table 2).

3.2. Clinical outcomes

3.2.1. Overall population

At 12 months after the index procedure for AMI with CS, MACE occurred in 278 (40.0 %) patients, with no significant differences among the four season groups (spring 68 (38.2 %); summer, 69 (44.5 %); autumn, 73 (40.1 %); and winter 68 (37.8 %) ($p = 0.587$). There were no significant differences in the individual components of MACE (cardiac death, $p = 0.630$; myocardial infarction, $p = 0.586$; any revascularization, $p = 0.507$; re-hospitalization due to heart failure, $p = 0.201$) at 12 months (Table 3). In cumulative Kaplan-Meier estimates, MACE showed no significant differences among the four season groups (log-rank $p = 0.515$) (Fig. 2A), and there were no significant differences between the other three groups compared to the spring group (log-rank $p = 0.175$ [summer group], 0.601 [autumn group], and 0.961 [winter group]). Cox proportional hazard models comparing the spring group to the other seasons revealed similar results (summer group, HR 1.26, 95 % CI 0.90–1.76, $p = 0.179$; autumn group, HR 1.09, 95 % CI 0.78–1.52, p

Table 1
Baseline clinical characteristics and In-hospital management.

	Overall population	Spring	Summer	Autumn	Winter	*p* value
	(n = 695)	(n = 178)	(n = 155)	(n = 182)	(n = 180)	
Age *(years)*	66.6 ± 12.6	67.3 ± 13.0	67.8 ± 12.6	65.1 ± 12.5	66.4 ± 12.1	0.183
Male	511 (73.5 %)	127 (71.3 %)	115 (74.2 %)	134 (73.6 %)	135 (75.0 %)	
BMI *(kg/m²)*	23.8 ± 3.4	23.5 ± 3.3	23.7 ± 3.2	24.1 ± 3.5	23.9 ± 3.6	0.351
Cardiovascular risk factors						
Hypertension	382 (55.0 %)	99 (55.6 %)	90 (58.1 %)	93 (51.1 %)	100 (55.6 %)	0.624
Diabetes mellitus	249 (35.8 %)	66 (37.1 %)	54 (34.8 %)	58 (31.9 %)	71 (39.4 %)	0.484
Dyslipidemia	209 (30.1 %)	59 (33.1 %)	49 (31.6 %)	58 (31.9 %)	43 (23.9 %)	0.210
Chronic kidney disease	58 (8.3 %)	21 (11.8 %)	9 (5.8 %)	18 (9.9 %)	10 (5.6 %)	0.090
Current smoker	247 (35.5 %)	58 (32.6 %)	60 (38.7 %)	68 (37.4 %)	61 (33.9 %)	0.607
Previous PCI	86 (12.4 %)	25 (14.0 %)	21 (13.5 %)	16 (8.8 %)	24 (13.3 %)	0.397
Previous myocardial infarction	88 (12.7 %)	30 (16.9 %)	19 (12.3 %)	15 (8.2 %)	24 (13.3 %)	0.105
Peripheral artery disease	21 (3.0 %)	7 (3.9 %)	5 (3.2 %)	5 (2.7 %)	4 (2.2 %)	0.810
Previous history of CABG	10 (1.4 %)	4 (2.2 %)	2 (1.3 %)	3 (1.6 %)	1 (0.6 %)	0.595
Previous history of stroke	55 (7.9 %)	13 (7.3 %)	11 (7.1 %)	15 (8.2 %)	16 (8.9 %)	0.920
Clinical presentation						0.085
NSTEMI	202 (29.1 %)	55 (30.9 %)	44 (28.4 %)	41 (22.5 %)	62 (34.4 %)	
STEMI	493 (70.9 %)	123 (69.1 %)	111 (71.6 %)	141 (77.5 %)	118 (65.6 %)	
Left ventricular ejection fraction *(%)*	36.5 ± 15.3	35.8 ± 14.3	34.6 ± 14.5	36.8 ± 16.6	38.7 ± 15.4	0.134
Systolic blood pressure, *mmHg*	74.6 ± 29.5	74.8 ± 27.2	76.6 ± 30.8	72.4 ± 30.6	74.7 ± 29.5	0.624
Diastolic blood pressure, *mmHg*	47.5 ± 20.0	48.2 ± 17.6	48.4 ± 21.8	45.4 ± 20.7	48.1 ± 19.8	0.432
Heart rate, beat/min	78.6 ± 32.7	80.6 ± 31.1	79.6 ± 33.9	74.3 ± 32.8	79.9 ± 33.2	0.248
Laboratory findings						
Hemoglobin, *g/dL*	13.1 ± 2.3	13.1 ± 2.2	13.2 ± 2.5	13.2 ± 2.3	13.1 ± 2.3	0.968
Creatinine, *mg/dL*	1.5 ± 1.3	1.7 ± 1.8	1.3 ± 0.9	1.4 ± 1.1	1.4 ± 1.2	0.060
Glucose, *mg/dL*	232.1 ± 119.5	226.0 ± 106.5	233.8 ± 122.0	236.5 ± 133.9	232.1 ± 114.3	0.872
Lactate, *mmol/L*	6.5 ± 4.5	6.6 ± 4.6	6.7 ± 4.8	7.2 ± 4.9	5.7 ± 3.7	0.105
Peak Troponin I, *ng/mL*	82.0 ± 170.0	77.2 ± 164.0	86.1 ± 135.7	111.2 ± 225.3	54.0 ± 128.9	0.019
SCAI shock classification[a]						0.523
C or D	328 (47.2 %)	86 (48.3 %)	66 (42.6 %)	85 (46.7 %)	91 (50.6 %)	
E	367 (52.8 %)	92 (51.7 %)	89 (57.4 %)	97 (53.3 %)	89 (49.4 %)	
Undergoing CPR	148 (21.3 %)	30 (16.9 %)	36 (23.2 %)	40 (22.0 %)	42 (23.3 %)	0.402
Vasoactive Inotropic Score	80.0 ± 155.4	70.9 ± 112.2	99.1 ± 193.4	80.6 ± 133.3	72.0 ± 175.0	0.329
IABP-SHOCK 2 score	2.2 ± 1.7	2.3 ± 1.7	2.2 ± 1.6	2.2 ± 1.9	2.2 ± 1.6	0.915
In-hospital management						
Multiple vasoactive drug use	369 (53.1 %)	101 (56.7 %)	79 (51.0 %)	90 (49.5 %)	99 (55.0 %)	0.482
Mechanical ventilation	380 (54.7 %)	89 (50.0 %)	89 (57.4 %)	99 (54.4 %)	103 (57.2 %)	0.472
Requiring RRT	123 (17.7 %)	33 (18.5 %)	25 (16.1 %)	36 (19.8 %)	29 (16.1 %)	0.753
Requiring IABP	210 (30.2 %)	51 (28.7 %)	43 (27.7 %)	51 (28.0 %)	65 (36.1 %)	0.257
Requiring ECMO	238 (34.2 %)	58 (32.6 %)	56 (36.1 %)	61 (33.5 %)	63 (35.0 %)	0.908

Data are n (%), mean ± standard deviation, or median (interquartile range).
CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenator; IABP = intra-aortic balloon pump; IABP-SHOCK = Intra-aortic Balloon Pump in Cardiogenic Shock; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RRT = renal-replacement therapy; SCAI = Society for Cardiovascular Angiography and Intervention; STEMI = ST-segment elevation myocardial infarction.
[a] SCAI shock classification "E" was defined as patients who requiring ECMO, undergoing CPR, lactate > 5 mmol/L, or vasoactive inotropic score >90.

Table 2
Angiographic and Procedural characteristics.

	Overall population	Spring	Summer	Autumn	Winter	*p* value
	(n = 695)	(n = 178)	(n = 155)	(n = 182)	(n = 180)	
Angiographic findings						
Culprit lesion location						0.050
LM	101 (14.5 %)	24 (13.5 %)	26 (16.8 %)	30 (16.5 %)	21 (11.7 %)	
LAD	292 (42.0 %)	74 (41.6 %)	67 (43.2 %)	71 (39.0 %)	80 (44.4 %)	
LCX	70 (10.1 %)	27 (15.2 %)	18 (11.6 %)	9 (4.9 %)	16 (8.9 %)	
RCA	232 (33.4 %)	53 (29.8 %)	44 (28.4 %)	72 (39.6 %)	63 (35.0 %)	
Culprit lesion TIMI flow grade, pre-PCI						0.482
0	403 (58.0 %)	106 (59.6 %)	90 (58.1 %)	107 (58.8 %)	100 (55.6 %)	
1	61 (8.8 %)	13 (7.3 %)	11 (7.1 %)	19 (10.4 %)	18 (10.0 %)	
2	104 (15.0 %)	28 (15.7 %)	27 (17.4 %)	29 (15.9 %)	20 (11.1 %)	
3	127 (18.3 %)	31 (17.4 %)	27 (17.4 %)	27 (14.8 %)	42 (23.3 %)	
Culprit lesion TIMI flow grade, post-PCI						0.287
0	10 (1.4 %)	4 (2.2 %)	0 (0.0 %)	1 (0.5 %)	5 (2.8 %)	
1	19 (2.7 %)	3 (1.7 %)	3 (1.9 %)	7 (3.8 %)	6 (3.3 %)	
2	89 (12.8 %)	26 (14.6 %)	15 (9.7 %)	24 (13.2 %)	24 (13.3 %)	
3	577 (83.0 %)	145 (81.5 %)	137 (88.4 %)	150 (82.4 %)	145 (80.6 %)	
Multivessel disease	536 (77.1 %)	131 (73.6 %)	121 (78.1 %)	145 (79.7 %)	139 (77.2 %)	0.572
Vessel disease						0.254
1-vessel disease	159 (22.9 %)	47 (26.4 %)	34 (21.9 %)	37 (20.3 %)	41 (22.8 %)	
2-vessel disease	295 (42.4 %)	61 (34.3 %)	71 (45.8 %)	87 (47.8 %)	76 (42.2 %)	
3-vessel disease	241 (34.7 %)	70 (39.3 %)	50 (32.3 %)	58 (31.9 %)	63 (35.0 %)	
Chronic total occlusion	141 (20.3 %)	40 (22.5 %)	29 (18.7 %)	31 (17.0 %)	41 (22.8 %)	0.449
Procedural characteristics						
Access site						0.713
Femoral artery	573 (82.4 %)	146 (82.0 %)	131 (84.5 %)	152 (83.5 %)	144 (80.0 %)	
Radial artery	122 (17.6 %)	32 (18.0 %)	24 (15.5 %)	30 (16.5 %)	36 (20.0 %)	
Implanted device						0.907
Second-generation DES	631 (90.9 %)	164 (92.1 %)	138 (89.0 %)	165 (91.2 %)	164 (91.1 %)	
Balloon angioplasty or thrombectomy only	54 (7.8 %)	13 (7.3 %)	15 (9.7 %)	13 (7.2 %)	13 (7.2 %)	
Others	9 (1.3 %)	1 (0.6 %)	2 (1.3 %)	3 (1.7 %)	3 (1.7 %)	
Number of stents	1.3 ± 0.8	1.3 ± 0.7	1.3 ± 0.9	1.3 ± 0.7	1.3 ± 0.8	0.699
Thrombus aspiration	235 (33.8 %)	54 (30.3 %)	46 (29.7 %)	70 (38.5 %)	65 (36.1 %)	0.228
Glycoprotein IIb/IIIa inhibitor	137 (19.7 %)	32 (18.0 %)	29 (18.7 %)	39 (21.4 %)	37 (20.6 %)	0.836
Staged PCI						0.447
Not done	634 (91.2 %)	167 (93.8 %)	144 (92.9 %)	161 (88.5 %)	162 (90.0 %)	
Incomplete revascularization	28 (4.0 %)	7 (3.9 %)	5 (3.2 %)	8 (4.4 %)	8 (4.4 %)	
Complete revascularization	33 (4.7 %)	4 (2.2 %)	6 (3.9 %)	13 (7.1 %)	10 (5.6 %)	
Treatment strategy						0.568
Single vessel complete revascularization	159 (22.9 %)	47 (26.4 %)	34 (21.9 %)	37 (20.3 %)	41 (22.8 %)	
Culprit only	369 (53.1 %)	83 (46.6 %)	80 (51.6 %)	109 (59.9 %)	97 (53.9 %)	
Multivessel PCI	98 (14.1 %)	26 (14.6 %)	25 (16.1 %)	22 (12.1 %)	25 (13.9 %)	
Index complete revascularization	69 (9.9 %)	22 (12.4 %)	16 (10.3 %)	14 (7.7 %)	17 (9.4 %)	
Door-to-balloon time <90 min	222 (97.8 %)	43 (100.0 %)	52 (98.1 %)	60 (95.2 %)	67 (98.5 %)	0.380

Data are n (%), mean ± standard deviation, or median (interquartile range).
CTO = chronic total occlusion; DES = drug-eluting stent; LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIMI = Thrombolysis in Myocardial Infarction.

Table 3
12-month follow-up clinical outcomes according to seasons when cardiogenic shock occurred.

	Total	Spring	Summer	Autumn	Winter	*p*-value
Overall population	(n = 695)	(n = 178)	(n = 155)	(n = 182)	(n = 180)	
MACE	278 (40.0 %)	68 (38.2 %)	69 (44.5 %)	73 (40.1 %)	68 (37.8 %)	0.587
Cardiac death	226 (32.5 %)	51 (28.7 %)	54 (34.8 %)	61 (33.5 %)	60 (33.3 %)	0.630
Myocardial infarction	16 (2.3 %)	5 (2.8 %)	5 (3.2 %)	4 (2.2 %)	2 (1.1 %)	0.586
Any revascularization	23 (3.3 %)	5 (2.8 %)	5 (3.2 %)	9 (4.9 %)	4 (2.2 %)	0.507
Re-hospitalization due to HF	39 (5.6 %)	14 (7.9 %)	11 (7.1 %)	8 (4.4 %)	6 (3.3 %)	0.201

HF = heart failure.

= 0.604; and winter group, HR 1.01, 95 % CI 0.72–1.41, $p = 0.961$) (Table 4).

3.2.2. Population after IPTW adjustment

After IPTW adjustment, the cumulative MACE rate compared by Kaplan-Meier estimates did not show a significant difference

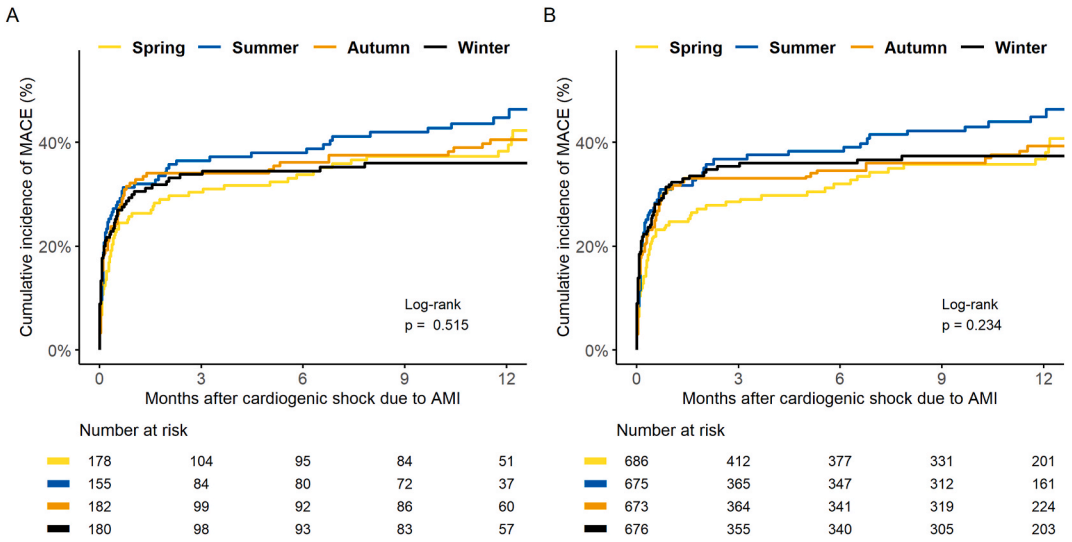


Fig. 2. Cumulative major cardiovascular event according to the season when the event occurred (A) Kaplan-Meier curves of 12-month MACE. (B) Kaplan-Meier curves of 12-month MACE with IPTW adjustment. Colors designate spring (yellow), summer (blue), autumn (orange), and winter (black). AMI = acute myocardial infarction, IPTW = inverse probability of treatment weighting, MACE = major adverse cardiovascular event (the composite of cardiac death, myocardial infarction, re-hospitalization due to heart failure, and any revascularization).

Table 4
Cox regression model comparing spring to other seasons for MACE.

	Before IPTW		After IPTW	
	HR (95 % CI)	***p*-value**	**HR (95 % CI)**	***p*-value**
Unadjusted				
Spring	1		1	
Summer	1.26 (0.90–1.76)	0.179	1.36 (0.97–1.90)	0.077
Autumn	1.09 (0.78–1.52)	0.604	1.12 (0.80–1.56)	0.522
Winter	1.01 (0.72–1.41)	0.961	1.13 (0.81–1.59)	0.469
Adjusted [a]				
Spring	1		1	
Summer	1.38 (0.98–1.96)	0.067	1.40 (0.98–1.99)	0.062
Autumn	1.37 (0.97–1.92)	0.073	1.26 (0.89–1.80)	0.193
Winter	1.18 (0.83–1.66)	0.360	1.18 (0.83–1.67)	0.356

AMI = acute myocardial infarction, HR = hazard ratio, IPTW = inverse probability of treatment weightingMACE = composite of cardiac death, myocardial infarction, any revascularization, re-hospitalization due to heart failure.

[a] Variables included in Cox model adjustment: age ≥65, gender, hypertension, diabetes mellitus, current smoking, serum creatinine ≥1.5 mg/dL, left ventricular ejection fraction <30 %.

among the four season groups (log-rank $p = 0.234$) (Fig. 2B). The Kaplan-Meier estimates of the other three seasons compared to spring after IPTW adjustment did not yield any significant results (log-rank $p = 0.096$ [summer], 0.564 [autumn], and 0.444 [winter]) (Fig. 3). Multivariate Cox-regression analysis after IPTW adjustment also showed no differences among the other three season groups compared to spring (summer group, HR 1.40, 95 % CI 0.98–1.99, $p = 0.062$; autumn group, HR 1.26, 95 % CI 0.89–1.80, $p = 0.193$; and winter group, HR 1.18, 95 % CI 0.83–1.67; $p = 0.356$). MACE occurrence appears to be higher numerically among patients presenting in the summer season compared to other seasons, but this difference did not reach statistical significance. (Table 4).

3.2.3. Subgroup analysis

We performed subgroup analyses to identify the association between seasonal temperateness (spring and autumn vs. summer and winter) and MACE in various situations. The prognostic effect of seasonal temperateness was consistent across subgroups regardless of age, sex, diabetes mellitus, left ventricular ejection fraction, multi-vessel disease, SCAI shock classification, vasoactive inotropic score, and requirement for renal replacement therapy (Fig. 4).

4. Discussion

This study compared the prognosis of CS caused by AMI according to season in a climate where the year is divided into four seasons using a dedicated, large-scale, multicenter real-world CS registry. Our main study finding was that there was no significant difference

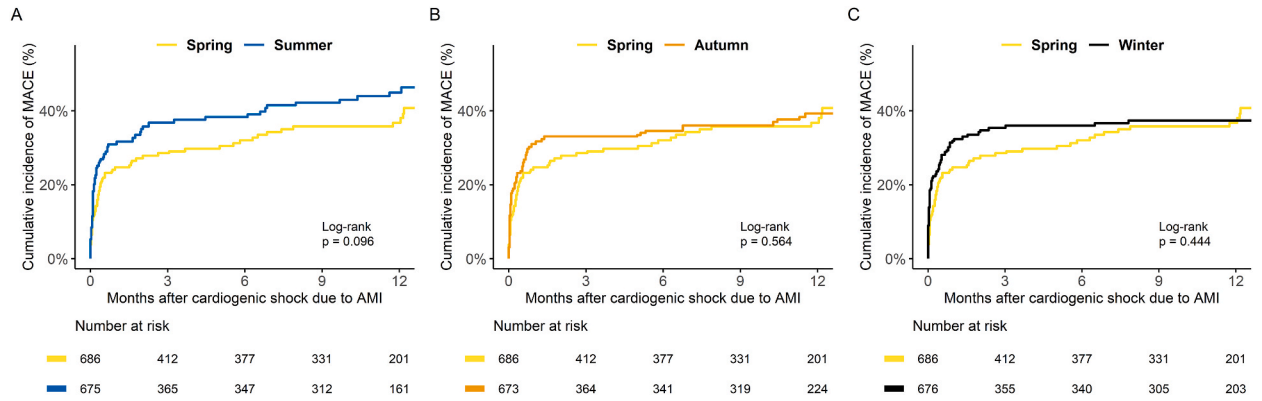


Fig. 3. Cumulative major cardiovascular event according to the season compared to spring Kaplan-Meier curves with IPTW adjustment of 12-month MACE according to season in AMI with cardiogenic shock. Colors designate spring (yellow), summer (blue), autumn (orange), and winter (black). AMI = acute myocardial infarction, IPTW = inverse probability of treatment weighting, MACE = major adverse cardiovascular event (the composite of cardiac death, myocardial infarction, re-hospitalization due to heart failure, and any revascularization).

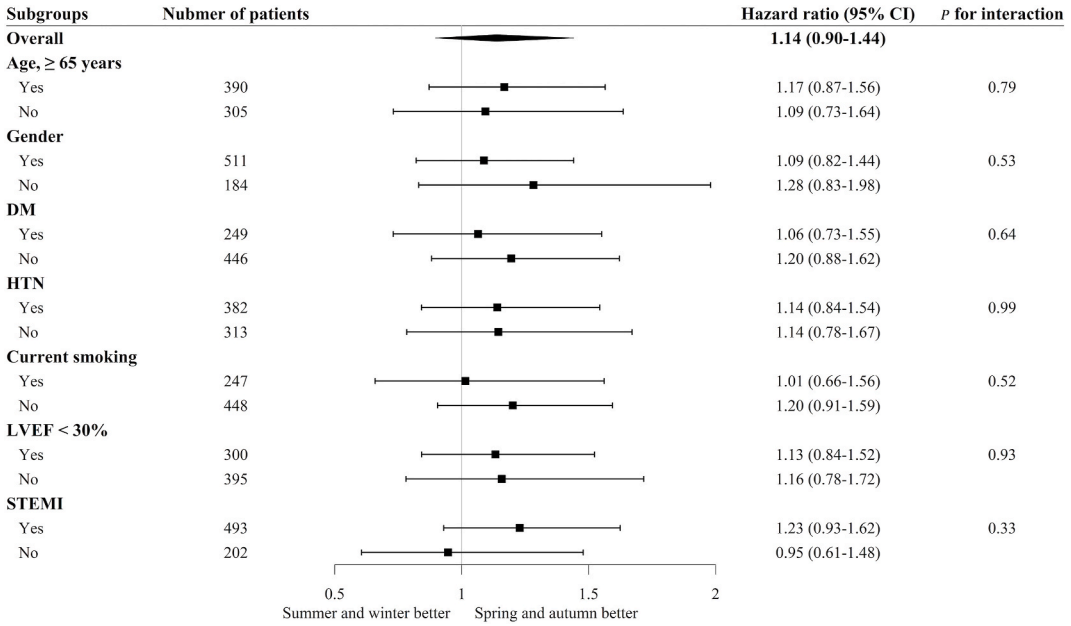


Fig. 4. Comparison of cardiovascular outcomes between Spring/autumn and Summer/winter Comparative adjusted hazard ratios of 12-month MACE comparing the spring/autumn and summer/winter subgroups. CI = confidence interval; DM = diabetes mellitus; HTN = hypertension; LVEF = left ventricular ejection fraction, STEMI = ST-segment elevation myocardial infarction.

in the risk of a composite of cardiac death, myocardial infarction, re-hospitalization due to heart failure, and repeat revascularization in the entire cohort of AMI with CS during 12 months after the index procedure according to the season in which the AMI occurred, and this was consistent across various subgroups. To the best of our knowledge, this is the first study about the prognostic effect of seasonal variation in AMI patients complicated by CS who received PCI.

Several studies have reported that temperature changes were associated with increased incidence and mortality of AMI [1–3]. The relationship between temperature and AMI can be explained by several mechanisms. Low temperatures induce systemic vasoconstriction or increase heart rate and blood pressure [2]. As a result of these physiologic responses, increased oxygen demand, increased sympathetic tone, and increased cardiac workload due to increased vascular resistance could contribute to the development of AMI and the increased incidence of post-MI complications. Increased renal diuresis in response to cold temperatures results in hematological abnormalities by increased and changed stickiness of platelets or red blood cells, blood viscosity, or abnormal condensations of fibrinogen [21], which may also contribute to the development of AMI [7,22]. Meanwhile, hot temperatures also activate the sympathetic nervous system and can increase heart rate, blood viscosity, and platelet and red blood cell counts [23–25], affecting coronary plaque instability, followed by AMI. Evidence has shown that mild temperatures have a lower frequency, morbidity, and mortality of

AMI than cold and heat [1]. For example, in Vietnam, a country that stretches from north to south and has various temperatures, incidence and hospitalizations related to AMI increased in the colder areas of the north or the hotter areas of the south compared to the areas with mild temperatures [26]. In South Korea, the annual average temperature ranges from 7 to 15 °C, and the annual average humidity ranges from 59 to 75 %. In August (the hottest month in South Korea), the average temperature is 21.6–29.8 °C, and humidity is 78 %. In January (the coldest month in South Korea), the average temperature is −5.7 to 4.4 °C, and humidity is 61.1 % [16]. Interestingly, spring or autumn in South Korea has milder temperatures than summer or winter, so it was assumed that there would be an improved clinical course of AMI with CS in spring and autumn compared to summer and winter; however, in all subgroup analyses, the spring and autumn seasons did not show a significantly different risk compared to summer and winter. In a study of time-series analysis with temperature changes in Germany from 1987 to 2014, it was found that AMI occurring in hot weather increased as the globe warmed during this period, supporting the relationship of heat to AMI [27]. In the UK, there are significantly more deaths from AMI during the winter compared to other seasons. However, with global warming, not only is the overall incidence of mortality of AMI decreasing, but also the difference in mortality of AMI between winter and other seasons is becoming less pronounced [28]. In our study, while the mild spring season showed a better trend in AMI, there was no significant difference between the seasonal groups. We anticipated that humidity might be another contributing factor to poor prognosis during summer and autumn, but it is not expected to have a significant effect during winter due to lower humidity level in South Korea. According to previous studies, there is no evidence that low humidity affects the incidence or outcome of AMI, although high humidity does seem to have such effects [3,26]. In western Europe, for example in Germany, the driest period is spring to summer (average relative humidity 67 %–71 %) [27], whereas in Korea, the humidity is the lowest in winter and highest in summer (winter 53–56 %; summer 81 %–87 %) [16]. Several European studies found that the incidence and prognosis of AMI were the worst in winter [2,7], which appears to be due to the combination of low temperature and high humidity. In this context, the prognosis is better than expected in winter among the four seasons in this study, presumed to be because winter in South Korea has a low temperature as a risk factor, but the humidity is not high. The seasonal variation in the effect of AMI on prognosis is more complex than anticipated. A detailed and pathophysiological comprehension is required to understand and manage AMI patients complicated by CS. Seasonal infection also could influence the occurrence of AMI, but the present study did not show prognostic differences between seasonal variations; this was similar to results of a previous study [29].

4.1. Study limitations

Despite the strengths of this study, which included the use of a large, multicenter, dedicated, recent real-world CS registry with minimal exclusion criteria, our study has some limitations. First, this was a non-randomized, retrospective, and observational study, and unmeasured confounding factors or selection bias may have significantly affected our results. In particular, the choice of revascularization and shock treatment strategies including mechanical circulatory support were at the operator's discretion, possibly introducing selection bias. Although we performed sensitivity analyses, including multivariable Cox regression and IPTW adjustment, to reduce the effects of potential confounders, we could not adjust for unmeasured variables. Second, because of the retrospective nature of our registry, we could not thoroughly identify any alterations in treatment strategies such as peri-procedural treatment or medical therapy in all study patients during follow-up. Moreover, we also did not have any information about socioeconomic variables, demographic factors such as socioeconomic status and residential area, or behavioral and psychosocial characteristics. Demographic population factors might affect temperature associated with the development of AMI and its clinical outcomes, especially in extreme weather. Therefore, due to lack of such data, we were unable to determine whether these factors could play a role in the prognostic differences observed. Third, although our registry is the largest to date, the cohort is still relatively small. Moreover, we evaluated CS patients who were treated only with PCI. CS patients treated with thrombolysis or CABG are not reflected in our results. The lack of significant interaction in certain subgroup analyses may have been due to this limited study sample. Therefore, the current results should be interpreted as hypothesis-generating and should be confirmed in a future, well-designed randomized trial. Fifth, the rate of nonfatal events was low relative to that of death during follow-up. Although we performed active follow-up, periodic site monitoring, and auditing of the source document in each individual center to ensure that all information was properly entered in the electronic case report form, we cannot rule out the possibility of missed events. Finally, our analysis was limited to 12 months of follow-up, and the true difference in the prognostic effect of season might not be apparent at 12 months. A longer follow-up duration may be necessary to confirm the clinical impact of season on adverse outcomes in AMI complicating CS.

5. Conclusions

In patients treated with PCI for AMI complicated by CS, there was no significant difference in the 12-month risk of MACE and secondary outcomes between the four seasonal groups. The similarity of 12-month MACE between the four groups was consistent across various subgroups. Based on our results, season does not seem to influence mid-term clinical outcomes in patients who underwent PCI for AMI with CS. Further investigation regarding the potential therapeutic implications of these findings should be considered.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Sodam Jung: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Woo Jin Jang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Wang Soo Lee:** Supervision, Software, Funding acquisition. **Ik hyun Park:** Supervision, Software, Funding acquisition. **Ju Hyeon Oh:** Supervision, Software, Funding acquisition. **Jeong Hoon Yang:** Supervision, Software, Funding acquisition. **Hyeon-Cheol Gwon:** Supervision, Software, Funding acquisition. **Chul-Min Ahn:** Supervision, Software, Funding acquisition. **Cheol Woong Yu:** Supervision, Software, Funding acquisition. **Hyun-Joong Kim:** Supervision, Software, Funding acquisition. **Jang-Whan Bae:** Supervision, Software, Funding acquisition. **Sung Uk Kwon:** Supervision, Software, Funding acquisition. **Hyun-Jong Lee:** Supervision, Software, Funding acquisition. **Jin-Ok Jeong:** Supervision, Software, Funding acquisition. **Sang-Don Park:** Supervision, Software, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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