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ORIGINAL ARTICLE

Association of onset-season with characteristics and long-term outcomes in acute myocardial infarction patients: results from the Japanese registry of acute myocardial infarction diagnosed by universal definition (J-MINUET) substudy

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Abstract
It is known that incidence and short-term mortality rate of acute myocardial infarction (AMI) tend to be higher in the cold season. The aim of our study was to investigate the association of onset-season with patient characteristics and long-term prognosis of AMI. This was a prospective, multicenter, Japanese investigation of 3,283 patients with AMI who were hospitalized within 48 h of symptom onset between July 2012 and March 2014. Patients were divided into 3 seasonal groups according to admission date: cold season group (December–March), hot season group (June–September), and moderate season group (April, May, October, and November). We identified 1356 patients (41.3%) admitted during the cold season, 901 (27.4%) during the hot season, and 1026 (31.3%) during the moderate season. We investigated the seasonal effect on patient characteristics and clinical outcomes. Baseline characteristics of each seasonal group were comparable, with the exception of age, Killip class, and conduction disturbances. The rates of higher Killip class and complete atrioventricular block were significantly higher in the cold season group. The 3-year cumulative survival free from major adverse cardiac events (MACE) rate was the lowest in the cold season (67.1%), showing a significant difference, followed by the moderate (70.0%) and hot seasons (72.9%) ($p < 0.01$). Initial severity and long-term prognoses were worse in patients admitted during the cold season. Our findings highlight the importance of optimal prevention and follow-up of AMI patients with cold season onset.

Keywords Acute myocardial infarction · Season · Temperature · Prognosis · Japan

Introduction

It is well known that there is a seasonal variation in the incidence of acute myocardial infarction (AMI) and the short-term mortality associated with it. Studies from Japan as well as outside Japan have demonstrated a higher risk of AMI during winter and spring [1–7]. Moreover, some of these studies have shown that short-term mortality is also the highest during winter and spring [6, 7]. However, the association between onset-season and patient characteristics and long-term mortality has not been well clarified. Additionally, the reasons underlying the seasonal variation in AMI are not well understood.

One of the possible reasons for the seasonal variation in AMI is suggested to be changes in temperature among seasons [2]. Therefore, the aim of this study was to evaluate the association of onset-season divided by average temperature with patient characteristics and long-term prognosis. From the nation-wide Japanese Registry of AMI patients (J-MINUET; the Japanese registry of acute

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Myocardial Infarction diagnosed by Universal dEfiniTion), compared the patient characteristics and long-term prognosis in three seasonal groups assigned according to monthly average temperature; cold season, hot season, and moderate season.

Materials and methods

Study design and subjects

The study design and primary results of the J-MINUET study have been published previously [8, 9]. Briefly, J-MINUET was a prospective observational multicenter study conducted in 28 institutions, in which 3283 consecutive AMI patients were enrolled between July 2012 and March 2014. AMI was diagnosed according to the European Society of Cardiology (ESC)/ACC Foundation (ACCF)/American Heart Association (AHA)/World Heart Foundation Task Force for the Universal Definition of Myocardial Infarction [10]. ST-segment elevation AMI was diagnosed in the presence of new ST elevation at the J point in at least 2 contiguous leads ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V2–3, and/or ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads [11, 12]. New or presumably new left bundle branch blocks were considered equivalent to ST-segment elevation myocardial infarction (STEMI). Up to 3 years of clinical follow-up data were obtained from a review of medical records, telephone contact, and mailed questionnaires. The J-MINUET study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of each participating institution.

Study populations and end points

According to monthly average temperature, we divided patients into three seasonal groups: the cold season group (December to March), the hot season group (July to September), and the moderate season group (April, May, October, and November). The primary outcome was major adverse cardiac events (MACE), including all-cause mortality, non-fatal MI, non-fatal stroke, heart failure, and urgent revascularization for unstable angina (UA) at 3 years. Non-fatal myocardial infarction (MI) included only types 1 and 2. Heart failure was defined as heart failure requiring hospital admission. The secondary endpoints included (1) death (2) composite of death and non-fatal MI (3) death, non-fatal MI, non-fatal stroke, and (4) composite of death, non-fatal MI, non-fatal stroke, and heart failure.

Statistical analysis

All continuous variables are described as their median values and interquartile range. All categorical variables are described using absolute and relative frequency distributions. Differences between groups of continuous variables were evaluated with the Kruskal–Wallis test. The Chi-square test was used for non-continuous and categorical variables. We conducted Kaplan-Meyer curves for patients in each seasonal group to the end points, and the differences between groups were assessed by log-rank test. Univariate and multivariate Cox proportional hazards models were used to calculate hazard ratios for all events and 95% confidence intervals. Throughout the present study, a p value of < 0.05 was considered significant. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Japan is an island nation in East Asia, which lies between 24° and 46° north latitude and from 123° to 146° east longitude. In most parts of Japan, the climate is a humid subtropical climate characterized by 4 distinct seasons: spring, summer, autumn, and winter. Among 28 participating institutions, 27 institutions were located in the humid subtropical climate, and only Sapporo Medical University is located in a hot summer continental climate. For the purpose of the present analysis, we defined three seasonal groups according to monthly average temperatures in Tokyo in 2012: the cold season group (December-March, < 10 °C), the hot season group (July–September, > 20 °C), and the moderate season group (April, May, October, and November, 10–20 °C). These three groups were consistent with the three groups defined based on k-means clustering in Okinawa (southernmost) and Sapporo (northernmost) (Fig. 1). Among the 3283 patients registered in the J-MINUET study, we identified 1356 cold season patients, 901 hot season patients, and 1026 moderate season patients.

Baseline characteristics and clinical status on admission

Baseline characteristics according to onset-season are shown in Table 1. Among the three seasonal groups, baseline characteristics were similar with the exception of age, the rate of dyslipidemia, and the use rate of angiotensin-converting enzyme inhibitors. The average age of patients was greater

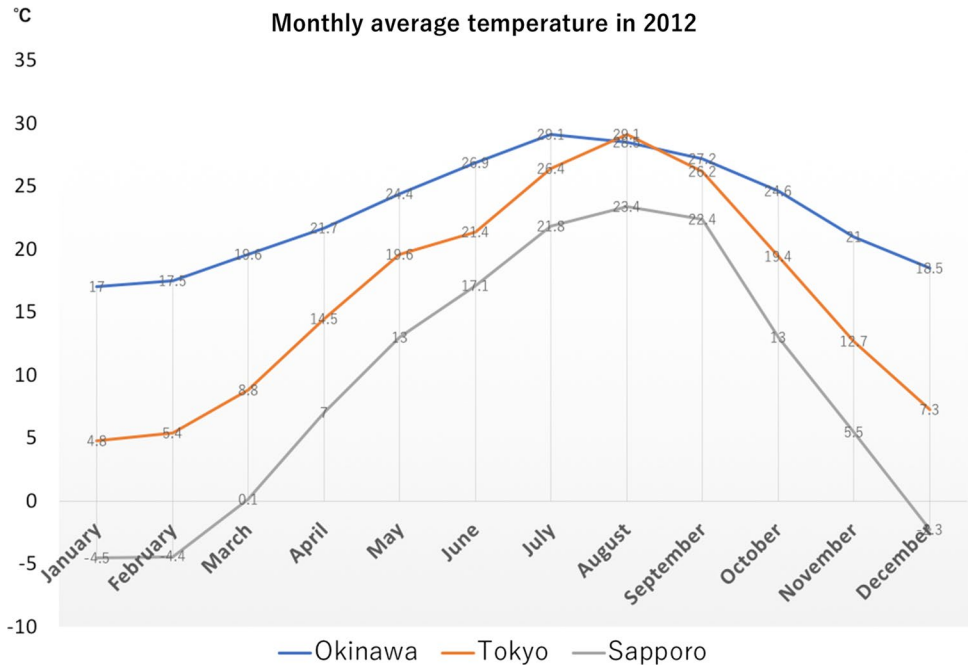

Fig. 1 Monthly average temperatures (Tokyo, Okinawa, Sapporo) in 2012

Table 1 Baseline characteristics according to onset-season

	Cold season group ($n=1356$)	Hot season group ($n=901$)	Moderate season group ($n=1026$)	*P* value
Age (years)	71 (61–78)	68 (60–77)	69 (61–78)	0.05
Male	1028 (75.8%)	689 (76.5%)	753 (73.4%)	0.24
Concomitant diseases				
Hypertension	884 (65.7%)	587 (65.7%)	694 (68.1%)	0.41
Diabetes	513 (38.2%)	293 (33.6%)	365 (36.3%)	0.08
Dyslipidemia	654 (48.8%)	477 (53.7%)	555 (54.5%)	0.01
CKD	215 (48.4%)	770 (38.3%)	184 (44.5%)	0.86
Current or ex-smoker	877 (67.3%)	558 (64.2%)	662 (65.9%)	0.54
Previous history				
Previous MI	156 (11.6%)	117 (13.0%)	122 (11.9%)	0.59
Previous PCI	192 (14.7%)	123 (14.7%)	157 (16.5%)	0.47
Previous CABG	39 (3.0%)	19 (2.3%)	32 (3.4%)	0.38
Prior stroke	150 (11.9%)	91 (10.9%)	102 (10.8%)	0.68
Previous PAD	57 (4.5%)	38 (4.8%)	43 (4.7%)	0.92
Medications at admission				
Aspirin	338 (24.9%)	248 (27.5%)	281 (27.4%)	0.27
P2Y12 antagonists	108 (8.0%)	72 (8.0%)	89 (8.7%)	0.80
OAC	58 (4.3%)	42 (4.7%)	45 (4.4%)	0.91
Calcium blockers	461 (34.0%)	303 (33.6%)	366 (35.7%)	0.59
β-Blocker	178 (13.1%)	131 (14.5%)	151 (14.7%)	0.47
ACE inhibitors	76 (5.6%)	76 (8.4%)	64 (6.2%)	0.03
ARBs	359 (26.5%)	242 (26.9%)	261 (25.4%)	0.76
Diuretics	125 (9.2%)	72 (8.0%)	95 (9.3%)	0.54
Statins	292 (21.9%)	212 (24.0%)	253 (24.9%)	0.22

CKD chronic kidney disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *PAD* peripheral artery disease, *OAC* oral anticoagulant, *ACEIs* angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker

in the cold season group. The clinical status of patients on admission is shown in Table 2. Vital signs, initial diagnosis, and time from onset to admission were similar among the three seasonal groups. However, the rate of higher Killip class (≥ 3) was significantly higher in the cold season group. With respect to electrocardiography, the rates of atrial fibrillation and ventricular arrhythmia were similar, whereas the rate of complete atrioventricular block was significantly higher in the cold season group.

Clinical management

Clinical management of each patient group is shown in Table 3. Overall, urgent coronary angiography was performed for more than 90% of patients in each season group and the rate was the highest in the cold season group. Initial thrombolysis in myocardial infarction (TIMI) 0 or 1 flow was observed at a similar rate in each season group. The rate of multi-vessel disease was the lowest in the hot season group. Primary percutaneous coronary intervention was performed for about 85% of patients in each group and the rate was relatively higher in the cold season group. Door to balloon (DTB) time was longer in the cold season group. Extracorporeal membrane oxygenation (ECMO) was used more in the cold season group. Rates of final TIMI 3 flow achievement and the performance rates of coronary artery bypass grafting and intra-aortic balloon pumping (IABP) were similar among the three seasonal groups. Prescribed medications at discharge were also similar among the three seasonal groups except for oral anticoagulants and calcium channel blockers.

3 years clinical outcomes

The cumulative 3-year survival rates free from MACE were the lowest in the cold season group (67.1%), followed by the moderate season group (70.0%) and the hot season group (72.9%), and these differences were significant ($p < 0.01$) (Fig. 2). The cumulative 30-day survival rates free from MACE were also the lowest in the cold season group (90.9%), followed by the hot season group (92.3%), and the moderate season group (93.0%), but the differences

Table 2 Clinical status, blood cell counts, and laboratory data according to onset-season

	Cold season group ($n = 1356$)	Hot season group ($n = 901$)	Moderate season group ($n = 1026$)	*P* value
Vitals				
SBP (mmHg)	136 (116–158)	138 (118–160)	140 (119–161)	0.15
HR (beats/min)	79 (66–92)	76 (65–90)	76 (64–90)	0.12
Killip class ≥ 3	236 (17.5%)	125 (13.9%)	132 (12.9%)	< 0.01
Electrocardiography				
Atrial fibrillation	58 (4.3%)	39 (4.3%)	51 (5.0%)	0.69
Ventricular tachycardia/fibrillation	68 (5.0%)	47 (5.2%)	64 (6.2%)	0.40
Complete AV block	65 (4.8%)	26 (2.9%)	25 (2.4%)	< 0.01
Typical symptom	1013 (78.6%)	675 (80.1%)	755 (79.1%)	0.73
Diagnosis				0.20
NSTEMI	941 (69.4%)	635 (70.5%)	686 (66.9%)	
STEMI	415 (30.6%)	266 (29.5%)	340 (33.1%)	
Type2 MI	59 (4.8%)	50 (6.0%)	46 (5.0%)	0.42
Time from onset to admission (min)	149 [66–364]	170 [75–432]	151 [70–389]	0.14
Blood cell counts				
WBC	9150 [7200–12000]	9000 [6900–11530]	9300 [7300–11700]	0.07
HGB	13.8 [12.3–15.0]	13.8 [12.4–15.1]	13.7 [12.3–15.2]	0.63
Platelet	20.3 [16.8–24.4]	19.9 [15.9–23.7]	20.0 [16.5–24.1]	0.06
Serum cholesterol				
Total cholesterol	184 [156–214]	183 [154–211]	182 [156–211]	0.51
HDL cholesterol	45 [38–54]	45 [37–52]	46 [38–55]	0.09
LDL cholesterol	116 [92–142]	115 [90–140]	113 [90–139]	0.29
Triglycerides	91 [60–148]	102 [65–159]	96 [61–149]	0.04

SBP systolic blood pressure, *HR* heart rate, *AV* atrioventricular, *NSTEMI* non-ST-elevated myocardial infarction, *STEMI* ST-elevated myocardial infarction, *MI* myocardial infarction, *WBC* white blood cell, *HGB* hemoglobin, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *Na* natrium, *K* potassium, *BNP* brain natriuretic peptide

Table 3 Clinical management according to onset-season

	Cold season group ($n=1356$)	Hot season group ($n=901$)	Moderate season group ($n=1026$)	P value
Urgent coronary angiography	1286 (94.8%)	821 (91.1%)	946 (92.6%)	<0.01
Initial TIMI 0/1 flow	751 (58.7%)	501 (61.4%)	581 (62.0%)	0.23
Multi-vessel disease	587 (45.8%)	325 (39.8%)	415 (44.1%)	0.02
Primary PCI	1177 (86.8%)	746 (83.0%)	865 (84.6%)	0.04
Door to balloon time (min)	76 [54–125]	73 [52–119]	73 [51–115]	0.07
Door to balloon time < 90 min	653 (61.4%)	453 (65.2%)	489 (63.5%)	0.27
Final TIMI 3 flow	1071 (91.3%)	679 (91.4%)	797 (92.8%)	0.44
Urgent CABG	29 (2.1%)	16 (1.8%)	22 (2.2%)	0.81
IABP	235 (17.6%)	152 (16.9%)	172 (16.8%)	0.84
ECMO	49 (3.7%)	25 (2.8%)	22 (2.1%)	0.09
Max CK (IU/L)	1480 [555–3153]	1437 [464–3195]	1416 [519–3165]	0.46
Medications at discharge				
Aspirin	1,151 (96.6%)	753 (95.4%)	857 (94.8%)	0.13
P2Y12 antagonists	926 (79.0%)	585 (78.7%)	697 (80.0%)	0.79
OAC	139 (11.7%)	119 (15.0%)	108 (11.9%)	0.06
Calcium blockers	264 (21.9%)	207 (26.1%)	194 (21.3%)	0.04
β-Blocker	804 (67.6%)	542 (69.6%)	614 (68.4%)	0.66
ACE inhibitors	590 (50.2%)	407 (53.1%)	482 (54.5%)	0.14
ARBs	346 (29.2%)	226 (29.3%)	236 (26.7%)	0.37
Diuretics	18 (1.5%)	13 (1.7%)	8 (0.9%)	0.33
Statins	1,034 (86.7%)	686 (87.2%)	788 (87.1%)	0.94

TIMI thrombolysis in myocardial infarction, *MI* myocardial infarction, *59PCI* primary coronary intervention, *CABG* coronary artery bypass grafting, *IABP* intra-aortic balloon pumping, *ECMO* extracorporeal membrane oxygenation, *CK* creatinine kinase, *OAC* oral anticoagulant, *ACEIs* angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker

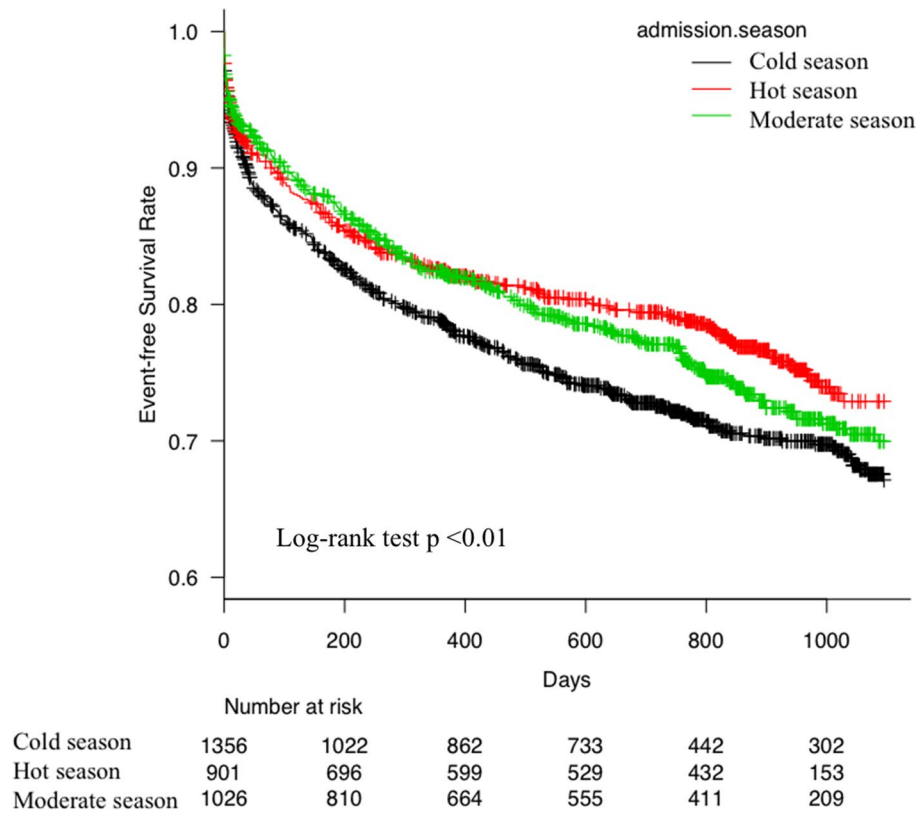

Fig. 2 Unadjusted Kaplan–Meier curves for the primary endpoint. The primary endpoint includes death, non-fatal myocardial infarction, non-fatal stroke, heart failure, revascularization for unstable angina

were not significant ($p = 0.184$). Kaplan–Meier curves for the secondary endpoints are shown in Fig. 3. The cumulative 3-year survival rate was the lowest in the cold season group (83.5%), followed by the hot season group (85.5%) and the moderate season group (87.0%), but these differences were not significant ($p = 0.08$). When comparing the cold season group with the moderate season group or the hot season group, the hazard ratios for MACE were 1.18 (95% CI 1.00–1.39) and 1.29 (95% CI 1.09–1.54), respectively. The hazard ratios for all-cause mortality were 1.29 (95% CI 1.01–1.63) and 1.22 (95% CI 0.95–1.55), respectively. Multivariate analysis adjusted for age or age and sex yielded similar trends (Table 4).

Discussion

From our multicenter, nation-wide registry data, we found some differences in patient characteristics and clinical management according to the onset-season. Overall, patients admitted in the cold season had the highest average age and presented with a severe clinical status with the higher Killip class and the higher rate of complete atrioventricular block. Moreover, patients who suffered AMI in the cold season showed poorer long-term clinical outcomes.

Previous studies have shown that the incidence of AMI and the short-term mortality risk were the highest during winter and spring, which is the equivalent to the cold season in our study. To the best of our knowledge, this is the first study to show that onset-season is associated with long-term prognosis of AMI patients. The reasons underlying the seasonal variations of AMI were not well understood. It has been proposed that cold temperature could be one of the

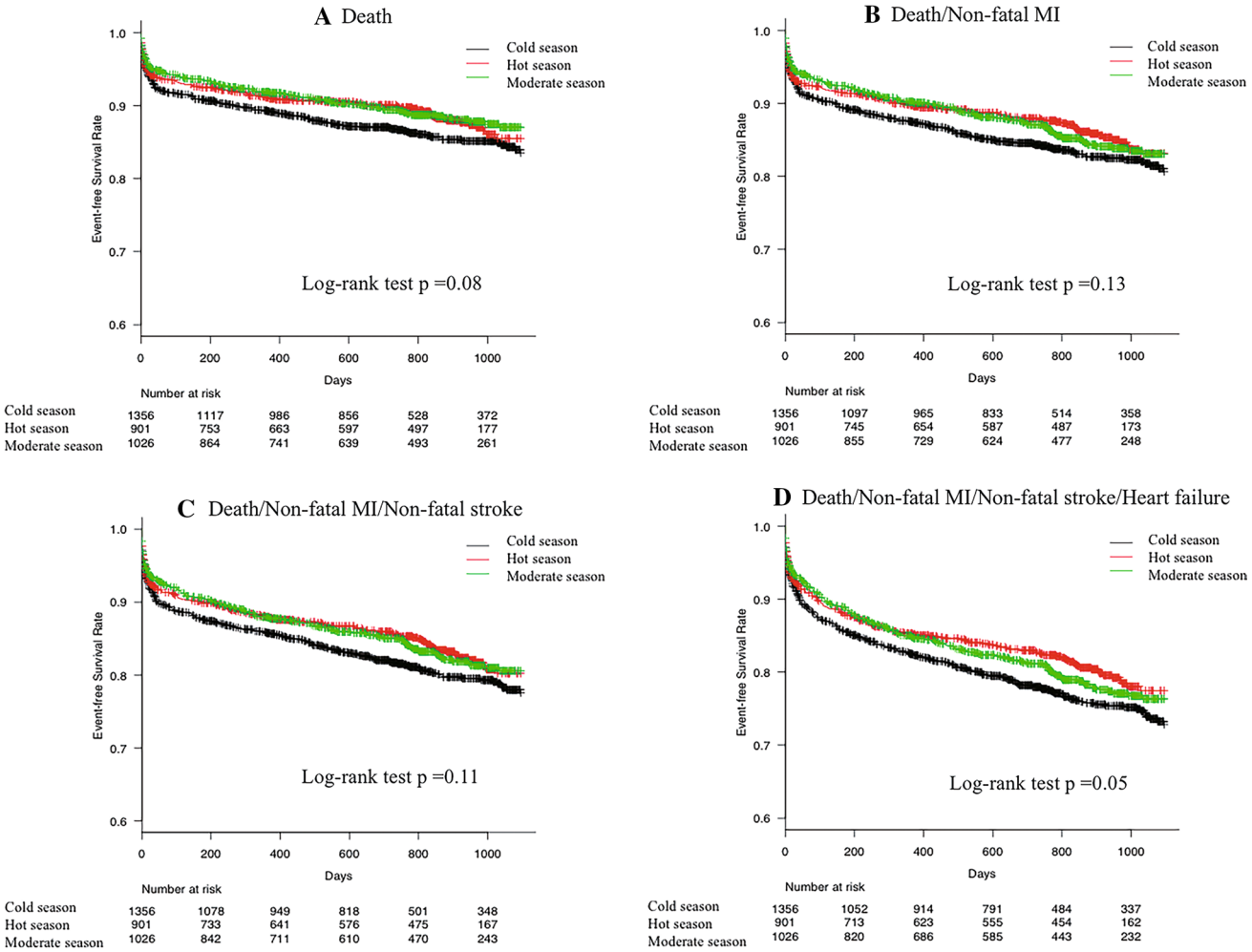

Fig. 3 Unadjusted Kaplan–Meier curves for the secondary endpoints. **a** Death; **b** death and non-fatal MI; **c** death, non-fatal MI and non-fatal stroke; **d** death, non-fatal MI, non-fatal stroke and heart failure

Table 4 Hazard ratio of MACE and death from acute myocardial infarction according to onset-season

	HR (95% CI)	*p* value	Age-adjusted HR (95% CI)	*p* value	Age–sex-adjusted HR (95% CI)	*p* value
MACE (3 year)						
Cold season (vs. moderate season)	1.18 (1.00–1.39)	< 0.05	1.15 (0.98–1.35)	0.09	1.15 (0.98–1.36)	0.09
Cold season (vs. hot season)	1.29 (1.09–1.54)	< 0.01	1.23 (1.03–1.46)	0.02	1.29 (1.03–1.46)	0.02
Death (3 year)						
Cold season (vs. moderate season)	1.29 (1.01–1.63)	0.04	1.25 (0.98–1.58)	0.07	1.26 (0.99–1.60)	0.06
Cold season (vs. hot season)	1.22 (0.95–1.55)	0.12	1.15 (0.92–1.44)	0.22	1.14 (0.89–1.45)	0.30

HR hazard ratio, *CI* confidential interval, *MACE* major adverse cardiac events (all-cause death, non-fatal myocardial infarction, non-fatal stroke, heart failure, urgent revascularizaion for unstable angina)

underlying reasons, given it has the following effects: (1) cardiovascular effects, such as increases in heart rate [13] and blood pressure [14, 15], and (2) the effects on blood and hemostasis, such as serum cholesterol and triglyceride levels [16–18], red blood cell counts, platelet counts [19], and coagulation factors [20, 21]. Although our study showed there were no statistical differences in heart rate, blood pressure, serum cholesterol, red blood cell counts, or platelet counts among the three seasonal groups, the changes of these parameters over time were not investigated. Not absolute values but the changes might affect the seasonal variation of AMI.

Case severity could be one of the reasons for poorer long-term clinical outcomes of patients who suffered AMI in the cold season. Our study showed an increased rate of patients with a higher Killip class or complete atrioventricular block in the cold season (Tables 2, 3). Previously, several reports have shown the cold season predominance of acute heart failure onset and have proposed similar underlying mechanisms to AMI [22–25]. Moreover, an increased rate of respiratory infections, especially those related to influenza, and an increase in alcohol consumption in winter have also been suggested to be the underlying causes [23]. Although there were no data regarding respiratory infections or alcohol consumption in our registry, it is assumed that the same is true in Japan [26]. Similarly, there are two reports showing the seasonal variations of bradyarrhythmias [27, 28]. Liu et al. demonstrated that extreme change in temperature was the most independent predictor of the development of advanced atrioventricular block and the peak occurrence was observed in spring [27]. These complications can exacerbate the patient initial condition and thus may lead to poorer long-term clinical outcomes.

Long-term clinical outcomes in AMI patients might reflect differences in case severity, but also differences in initial patient care. Our registry data showed that there were no significant differences in medications administered for secondary prevention according to onset-season. On the other hand, rates of intervention or ECMO were the highest in the cold season. An increase in the use of ECMO suggests that more critically ill patients admitted in the cold season. In our registry, the indications for intervention were at the discretion of the treating physicians and have not been reported. Therefore, the reason for the high rate of intervention in the cold season was unfortunately unclear in the present analysis. In addition, DTB time was numerically longer in the cold season group. One of the possible explanations for delayed DTB time is that patients who are in a more severe condition may require resuscitation procedures such as intubation, IABP, or ECMO prior to the intervention, and this caused delays. Namely, multiple factors related to the cold temperatures not only trigger AMI onset but also worsen the patient initial condition, affecting the initial patient care, and ultimately may lead to poorer long-term prognosis. Therefore, the present analysis suggests that the preventative approach, including better protection against cold temperatures and respiratory infections, is crucial for improvement of clinical outcomes in patients at risk of AMI. Moreover, careful follow-up and management may be required in patients who suffer AMI in the cold season.

Limitations

The present study was a sub-analysis of the J-MINUET study, which is a large-scale, prospective, nation-wide, multicenter registry describing the clinical presentation, treatment, and outcomes of Japanese patients with AMI in the contemporary era. However, it has certain limitations. First, since the J-MINUET is not a random sample of all Japanese hospitals and the participating institutions are regional core centers that tend to be capable of advanced medical management, there might have been a selection bias for enrolled patients. Second, initial diagnosis and adverse clinical events were not centrally adjudicated in our registry. All diagnoses and events were identified by the patient's physician and confirmed by the principal investigator of each hospital. Therefore, there is a possibility of inaccurate diagnosis and identification of clinical events. Finally, although all but one

participating institutions belong to the same climate zone, the institutions are located all across the nation and the seasonal pattern might slightly differ among these institutions, which could affect the seasonal effect on patient characteristics and long-term prognosis. Although the increased incidence of AMI and the increased short-term mortality in the cold season are observed in various climate zones [2, 6, 7, 29–32], a few observational studies in some other regions failed to detect the seasonal variation [33, 34]. Moreover, in these studies, it has not been well studied whether the effects of cold temperature might differ depending on the regions or the climate zones. Therefore, further investigation is needed to confirm that our findings are consistent in various regions in Japan as well as in other countries with different climate zones.

Conclusion

In this large national registry, the initial patient severity and long-term prognosis were the worst in AMI patients admitted in the cold season. The present study supports the hypothesis that cold season onset of AMI might affect patient characteristics and long-term prognosis. These data might provide insight into the optimal prevention and follow-up of AMI patients with cold season onset. Further investigations studying the seasonal variations of AMI would give us more insight into the unknown pathophysiology and triggers of AMI.

Conflict of interest

Kengo Tanabe: remuneration; Abbott Vascular, Daiich-Sankyo, Tanabe Mitsubishi Pharma. Yukio Ozaki: research fund; Bayer, Research Institute for Production Development. Scholarship fund; Daiichi-Sankyo, Dainippon Sumitomo. Junya Ako: remuneration; Tanabe Mitsubishi Pharma, Daiichi-Sankyo, Actelion, Sanofi, Takeda Pharmaceutical, Mochida Pharmaceutical, Shionogi, Kaneka, Astra Zeneca, Astellas Pharma, Volcano, Terumo, Eisai, Bristol-Myers Squibb, St. Jude Medical, Kyowa Hakko Kirin, Pfizer, Ono Pharmaceutical, Abbott Vascular Japan, Toa Eiyo, JIMRO, Kissei, Sumitomo Dainippon Pharma. Scholarship funds: Astellas Pharma, Mediphysics, Ono Pharmaceutical, Bristol-Myers Squibb, Pfizer, Behringer Ingelheim, Kyowa Hakko Kirin, Bayer, Eisai, Teijin, Kowa Pharmaceutical, Mochida Pharmaceutical, Abbott Vascular Japan, Medtronic Japan, Asahi Intec, Astra Zeneca, Sumitomo Dainippon Pharma, Otsuka Pharmaceutical, Tanabe Mistubishi Pharma, Takeda Pharmaceutical, Japan Lifeline. Yoshihiko Saito: scholar fund; Takeda Pharmaceutical, Teijin Pharma, Ono Pharmatical, Tanabe Mitsubishi, Eisai, ZERIA Pharmaceutical, Shionogi, Otsuka Pharmaceutical, Dainippon Sumitomo Pharma, Kyowa Hakko Kirin, Astellas, Daiichi-Sankyo, Boston Scientific Japan. Affiliation with endowed department; MSD, a subsidiary of Merck & Co. Wataru Shimizu: remuneration; Daiichi-Sankyo, Boehringer Ingelheim Japan, Bayer, Bristol-Myers Squibb, Ono Pharmaceutical, Pfizer. Scholarship fund; Daiichi-Sankyo, Boehringer Ingelheim Japan, Ono Pharmaceutical, Otsuka Pharmaceutical, Eisai, Tanabe Mitsubish Pharma, Astellas Pharma, St. Jude Medical. Kazuo Kimura: remuneration; Astra Zeneca, Toa Eiyo, Bayer, Daiichi-Sankyo. Scholarship fund; MSD, Daiichi-Sankyo, Ono Pharmaceutical, Pfizer, Bayer, Takeda Pharmaceutical, Boehringer Ingelheim Japan, Tanabe Mitsubishi, Astellas. Yoshihiko Saito: remuneration; Otsuka Pharmaceutical, Kowa Pharmaceutical, Daiichi-Sankyo, Tanabe Mitsubishi Pharma, Pfizer Japan, Novartis Pharma. Kenichi Tsujita: remuneration; Bayer, MSD, Sanofi, Amgen Astellas BioPharma, Daiichi-Sankyo. Research funds; AstraZeneca. Scholarship fund; Astellas, Bayer, Boehringer Ingelheim Japan, Boston Scientific Japan, Chugai, Daiichi-Sankyo, Eisai, Kowa, Tanabe Mistsubishi, MSD, Pfizer, Sanofi, Shionogi, Takeda Pharmaceutical. Masaharu Ishihara: remuneration; Bayer, MSD, Astra Zeneca, Astellas. Scholarship fund; Abbott Vascular, Boston Scientific, Sanofi, MSD, Astellas, Bayer, Pfizer, Daiichi-Sankyo, MID, Goodman.

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