Association of ambient temperature and acute heart failure with preserved and reduced ejection fraction

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Abstract

Aims Evidence on the association between ambient temperature and the onset of acute heart failure (AHF) is scarce and mixed. We sought to investigate the incidence of AHF admissions based on ambient temperature change, with particular interest in detecting the difference between AHF with preserved (HFP EF), mildly reduced (HFmrEF), and reduced ejection fraction (HFrEF).

Methods and results Individualized AHF admission data from January 2015 to December 2016 were obtained from a multicentre registry (Tokyo CCU Network Database). The primary event was the daily number of admissions. A linear regression model, using the lowest ambient temperature as the explanatory variable, was selected for the best-estimate model. We also applied the cubic spline model using five knots according to the percentiles of the distribution of the lowest ambient temperature. We divided the entire population into HFpEF + HFmrEF and HFrEF for comparison. In addition, the in-hospital treatment and mortality rates were obtained according to the interquartile ranges (IQRs) of the lowest ambient temperature (IQR1 <5.5°C; IQR2 5.5–13.3°C; IQR3 13.3–19.7°C; and IQR4 >19.7°C). The number of admissions for HFpEF, HFmrEF and HFrEF were 2736 (36%), 1539 (20%), and 3354 (44%), respectively. The lowest ambient temperature on the admission day was inversely correlated with the admission frequency for both HFpEF + HFmrEF and HFrEF patients, with a stronger correlation in patients with HFpEF + HFmrEF ($R^2 = 0.25$ vs. $0.05$, $P < 0.001$). In the sensitivity analysis, the decrease in the ambient temperature was associated with the greatest incremental increases in HFpEF, followed by HFmrEF and HFrEF patients, with a stronger correlation in patients with HFpEF + HFmrEF ($R^2 = 0.25$ vs. 0.05, $P < 0.001$). In the sensitivity analysis, the decrease in the ambient temperature was associated with the greatest incremental increases in HFpEF, followed by HFmrEF and HFrEF patients (3.5% vs. 2.8% vs. 1.5% per $–1^\circ$C, $P < 0.001$), with marked increase in admissions of hypertensive patients (systolic blood pressure $>140$ mmHg vs. $140–100$ mmHg vs. $<100$ mmHg, 3.0% vs. 2.0% vs. 0.8% per $–1^\circ$C, $P$ for interaction <0.001). A mediator analysis indicated the presence of the mediator effect of systolic blood pressure. The in-hospital mortality rate (7.5%) did not significantly change according to ambient temperature ($P = 0.62$).

Conclusions Lower ambient temperature was associated with higher frequency of AHF admissions, and the effect was more pronounced in HFpEF and HFmrEF patients than in those with HFrEF.

Keywords Acute heart failure; Ambient temperature; Heart failure with preserved ejection fraction; Heart failure with reduced ejection fraction; Hypertension

Received: 14 August 2021; Revised: 13 May 2022; Accepted: 31 May 2022
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Introduction

Climate change has been considered potentially the greatest threat to human health of the 21st century. Numerous studies have demonstrated that the ambient temperature is associated with the occurrence of cardiovascular events such as acute coronary syndrome. Further, both the lowering and the elevation of the ambient temperature are known to influence acute events related to heart failure (HF).
However, HF is a complex syndrome that encompasses a broad spectrum of background medical conditions and different phenotypes. In the recent years, clinical practice guidelines have classified HF as HF with preserved ejection fraction (HFP EF), mildly reduced ejection fraction (HFrEF), and reduced ejection fraction (HFrEF) according to left ventricular ejection fraction. Whereas cardiac function is directly responsible for the prognosis of patients with HFrEF, non-cardiac comorbidities accompanied by venous and arterial endothelial dysfunction are thought to play a substantial role in HFP EF patients. In addition, there is an overlap of clinical characteristics and prognosis of HFP EF and HFrEF in the HFrEF patients. Given that changes in the ambient temperature have been shown to affect vascular function, differences in the pathophysiology of HFP EF and HFrEF may lead to different responses to the meteorological changes within individual patient groups.

We sought to investigate the association between the ambient temperature and the incidence of acute HF (AHF) hospital admissions according to its phenotypes, using the contemporary, prospective, and multicentre registry in Tokyo, constructed in collaboration with emergency medical services. In addition, we analyzed the effect of the ambient temperature according to the patient background and mode of onset of AHF.

**Methods**

This was a retrospective observational study using the Tokyo Cardiac Care Unit (CCU) Network Database. The design of the Tokyo CCU Network Database has been previously reported. Briefly, this is an ongoing multicentre registry that prospectively collects information on emergency admissions to acute cardiac facilities of major hospitals in the Tokyo metropolitan area (72 facilities), serving a population of 13 million individuals. Ethical approval was obtained from the Institutional Review Board of Tokyo CCU Network Scientific Committee. The investigation conforms with the principles outlined in the Declaration of Helsinki (Br Med J 1964; ii: 177). All patients and/or their legal representatives provided written informed consent during their admission according to the protocol.

**Data collection**

For the present analysis, we identified 9336 consecutive patients with AHF, who were hospitalized via emergency medical services between 1 January 2015 and 31 December 2016. Individual patient information was collected by the investigators in each facility. Patients with acute coronary
syndrome were not enrolled in the present study because they were registered separately in alternate database. Patients with uncommon HF aetiologies including pericarditis (n = 48), endocarditis (n = 59), myocarditis (n = 27), cardiac tamponade (n = 25), and Takotsubo cardiomyopathy (n = 3), and whose ejection fraction (EF) data were inaccessible (n = 1545) were excluded (Figure 1). In addition, we collected meteorological data from the database of the Japan Meteorological Agency.

Outcome and definitions of variables

The primary outcome was the number of AHF admissions per day. The diagnosis of AHF was made by cardiologists at each institution based on Framingham criteria. The outcome was assessed and compared between the HFrEF + HFmrEF and HFrEF groups. HFrEF, HFmrEF, and HFrEF were defined as the left ventricular EF on admission ≥50%, 40–49%, and <40%, respectively. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Equation for Japanese Patients.

Geography and atmospheric characteristics of Tokyo

The city of Tokyo is situated in the central region of Japan, with a population of 13 million. The monthly change in the number of population was within 0.9% during the study period. Tokyo observes significant variation in weather, and hence, patients subjected to varying temperatures through the seasons served as a suitable patient-based dataset for this investigation; the city is in a subtropical region with distinct climate differences in four seasons (winter, December–February; spring, March–May; summer, June–August; fall, September–November). The meteorological background of Tokyo is summarized in Supporting information Table S1.

Statistical analysis

Results are expressed as mean ± standard deviation or median with interquartile range for continuous variables and as numbers and percentages for categorical variables. The unpaired t test or Mann–Whitney U test was used to compare continuous variables, Pearson’s χ² test was used to compare binary and nominal categorical variables, and one-way analysis of variance was used to compare continuous variables among the groups >2.

To estimate the association between the ambient temperature and AHF admission per day, we applied the cubic spline model using five knots according to the percentiles of the distribution of the lowest ambient temperature, the 5th, 22.5th, 50th, 77.5th, and 95th percentiles. In addition, a linear regression model and a Poisson regression model were compared based on the Akaike information criterion and the Bayesian information criterion (Table S2). We also considered the highest, average, and lowest ambient temperatures on the current day for explanatory variables and compared them. Consequently, a linear regression model, using the lowest ambient temperature as the explanatory variable, was selected for the best-estimate model.

Percent-incidence of AHF admission was defined as the number of admissions per day divided by the average number of the admissions per day during the study period. The change in percent-incidence by the lowest ambient temperature was analyzed using a linear regression model according to the following subgroups: EF (HFrEF + HFmrEF and HFrEF), sex, age (≥75 and <75 years), body mass index (≥25 and <25 kg/m²), systolic blood pressure (sBP) (<100, 100–140, and >140 mmHg), estimated glomerular filtration rate (<45 and ≥45 mL/min/1.73 m²), haemoglobin (≥11 and <11 mg/dL), C-reactive protein level (≥1 and <1 mg/dL), B-type natriuretic protein (BNP) (≥800 and <800 pg/mL), comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, atrial fibrillation (Af) at presentation, prior HF hospitalization, and aetiology (ischaemic heart disease and other aetiologies). The change in percent-incidence by the lowest ambient temperature was also analyzed for each HFrEF, HFmrEF, and HFrEF groups and the groups divided by EF ranges (<30%, 30–40%, 40–50%, 50–60% >60%). In addition, sensitivity analysis was performed for the subdivided groups according to age, estimated glomerular filtration rate, haemoglobin, C-reactive protein, and BNP (Table S3). Further, a mediator analysis was performed to estimate the mediator effect of sBP on the relationship between temperature change and AHF admissions (Table S4).

The in-hospital management and mortality rates were obtained by the interquartile range (IQR) of the lowest ambient temperature (IQR1 <5.5°C; IQR2 5.5–13.3°C; IQR3 13.3–19.7°C; and IQR4 >19.7°C). All P values were two sided, and P values <0.05 were considered statistically significant. The cubic spline model was carried out using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). All the other analyses were performed using SPSS ver. 25.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics and meteorological information

Patient characteristics are shown in Table 1. The total number of AHF incidents in the study period was 7629.
The daily median number of AHF admissions was 10 (7–13) per day. Compared with HFrEF patients, the patients with HFpEF and HFmrEF were older, more likely to be female, and demonstrated higher sBP at the time of admission. Patient characteristics are shown according to the IQRs of the lowest ambient temperature in Table S5. The number of HFpEF patients increased in the lowest temperature range (39%) and decreased in the highest temperature range (32%). The median BNP value was higher in the highest temperature range. The proportion of patients presenting with atrial fibrillation and the prevalence of the

| Variables                                | All patients (n = 7629) | HFpEF + HFmrEF (n = 4275) | HFrEF (n = 3354) |
|------------------------------------------|-------------------------|---------------------------|------------------|
| Incidents per day                        | 10 (7–13)               | 5 (4–8)                   | 4 (3–6)          |
| Male                                     | 4425 (58)               | 2059 (48)                 | 2366 (71)        |
| Age, years                               | 76 ± 13                 | 79 ± 12                   | 73 ± 14          |
| LVEF, %                                  | 43 ± 18                 | 54 ± 16                   | 28 ± 7           |
| Body mass index                          | 22.3 ± 4.8              | 22.4 ± 4.8                | 22.4 ± 4.8       |
| sBP at admission, mmHg                   | 151 ± 38                | 154 ± 39                  | 145 ± 36         |
| Laboratory findings                      |                         |                           |                  |
| Haemoglobin, g/dL                        | 11.9 (10.3–13.7)        | 11.3 (9.9–12.9)           | 12.6 (10.9–14.3) |
| Serum creatinine, mg/dL                  | 1.13 (0.84–1.70)        | 1.10 (0.80–1.70)          | 1.18 (0.9–1.74)  |
| eGFR, mL/min/1.73 m²                     | 43 (27–76)              | 42 (26–60)                | 44 (28–59)       |
| CRP, mg/dL                               | 0.7 (0.2–2.3)           | 0.7 (0.2–2.6)             | 0.7 (0.2–2.3)    |
| BNP, pg/mL                               | 769 (434–1385)          | 626 (332–1126)            | 996 (608–1705)   |
| Comorbidities                            |                         |                           |                  |
| Hypertension                             | 4774 (63)               | 2851 (67)                 | 1923 (57)        |
| Diabetes                                 | 1756 (23)               | 954 (22)                  | 802 (24)         |
| COPD                                     | 472 (6)                 | 267 (6)                   | 205 (6)          |
| Atrial fibrillation                      | 2753 (36)               | 1700 (40)                 | 1053 (31)        |
| Prior HF hospitalization                  | 3115 (41)               | 1698 (39)                 | 1457 (43)        |
| Aetiology                                |                         |                           |                  |
| Ischaemic aetiology                      | 1905 (25)               | 829 (19)                  | 1076 (32)        |
| Non-ischaemic aetiology                  | 5724 (75)               | 3446 (81)                 | 2278 (68)        |

BNP, B-type natriuretic protein; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; sBP, systolic blood pressure.

Values are presented as mean ±SD, median (interquartile range) or n (%).
arrhythmia-induced cardiac failure were not significantly different between the IQRs.

The change in the ambient temperatures and the number of AHF incidents in Tokyo are shown in Figure S1. The average, lowest, and highest temperatures were 16.5°C, 12.8°C, and 20.9°C, respectively. The lowest ambient temperature demonstrated the strongest negative correlation with the increase in the incidence of AHF ($R^2 = 0.24$, $P < 0.001$; Table S2).

Figure 3 Forest plots comparing the percent change in acute heart failure (HF) admissions. The plots represent the percent change in HF admissions per 1°C decrease in the lowest temperature on the current day according to specific subgroups (Figure 3A), and EF range (Figure 3B). The vertical solid line corresponds to an equal change. The horizontal solid lines are 95% confidence intervals. BNP, B-type natriuretic protein; CRP, C-reactive protein; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with reduced ejection fraction.
Ambient temperature and the number of HFpEF, HFmrEF and HFrEF incidents

The association between the lowest ambient temperature and the admissions of HFpEF + HFmrEF and HFrEF is shown in Figure 2. There was a negative and approximately linear correlation between the lowest ambient temperature and the incidence of AHF. This correlation was more apparent for HFpEF + HFmrEF than for HFrEF patients. In addition, linear regression analysis demonstrated a significantly stronger correlation in HFpEF + HFmrEF than in HFrEF ($R^2 = 0.25$ vs. 0.05, $P < 0.001$, $\beta$ coefficient $-0.50$ vs. $-0.25$, $P$ for interaction $<0.001$). Figure 3A represents the change in percent-incidence of AHF admission per 1°C decrease in the lowest ambient temperature by specific subgroups. The increment in percent-incidence of AHF admission was 2.5% per 1°C [95% confidence interval (CI), 2.2–2.8%], and was significantly larger in HFpEF + HFmrEF than in HFrEF patients [percent change (95% CI), 3.3 (2.8–3.7) vs. 1.5 (1.0–2.0) percent per 1°C, $P < 0.001$].

Sensitivity analysis

As compared with HFrEF patients, HFpEF + HFmrEF patients demonstrated a larger increase in the percent-incidence of AHF admission with decreasing ambient temperature in all subgroups (Figure 3A), including patients with a history of hypertension ($P < 0.001$) and those without a history of hypertension ($P = 0.008$).

Of note, the patients presenting with hypertensive condition demonstrated larger incremental change irrespective of HFpEF + HFmrEF or HFrEF ($P$ for interaction = 0.017), and female patients showed a trend of larger increment ($P$ for interaction = 0.058: Figure S2). There was no significant difference in the incremental change between patients with and those without a history of hypertension ($P$ for interaction = 0.59).

Table 2 In-hospital management and mortality according to temperature range

| In-hospital management | All patients | IQR1 | IQR2 | IQR3 | IQR4 | $P$ value |
|------------------------|-------------|------|------|------|------|-----------|
| Inotropic              |             |      |      |      |      |           |
| All patients           | 1383 (20)   | 429 (19) | 351 (19) | 301 (20) | 302 (22) | 0.040     |
| HFpEF + HFmrEF         | 448 (12)    | 157 (12) | 113 (11) | 102 (12) | 76 (12)  | 0.92      |
| HFrEF                  | 935 (30)    | 272 (29) | 238 (29) | 199 (29) | 226 (33) | 0.21      |
| Vasodilator            |             |      |      |      |      |           |
| All patients           | 4774 (68)   | 1613 (71) | 1251 (68) | 1012 (66) | 898 (67)  | 0.011     |
| HFpEF + HFmrEF         | 2665 (69)   | 956 (71) | 676 (66) | 564 (67) | 469 (71)  | 0.028     |
| HFrEF                  | 2109 (67)   | 657 (70) | 575 (69) | 448 (65) | 429 (62)  | 0.005     |
| IV loop diuretics      |             |      |      |      |      |           |
| All patients           | 5642 (80)   | 1859 (81) | 1485 (80) | 1224 (80) | 1074 (80) | 0.57      |
| HFpEF + HFmrEF         | 3127 (81)   | 1095 (81) | 819 (80) | 685 (81) | 528 (80)  | 0.85      |
| HFrEF                  | 2515 (80)   | 764 (81) | 666 (80) | 539 (78) | 546 (80)  | 0.44      |
| Intubation             |             |      |      |      |      |           |
| All patients           | 529 (6.9)   | 184 (7.4) | 134 (6.7) | 106 (6.4) | 105 (7.1) | 0.58      |
| HFpEF + HFmrEF         | 258 (6.0)   | 95 (6.4) | 64 (5.7) | 55 (5.9) | 44 (6.0)  | 0.89      |
| HFrEF                  | 271 (8.1)   | 89 (8.9) | 70 (7.9) | 51 (7.0) | 61 (8.3)  | 0.54      |
| NPPV                   |             |      |      |      |      |           |
| All patients           | 3058 (40)   | 971 (39) | 793 (40) | 696 (42) | 598 (41)  | 0.36      |
| HFpEF + HFmrEF         | 1643 (38)   | 574 (39) | 418 (37) | 369 (40) | 282 (36)  | 0.78      |
| HFrEF                  | 1415 (42)   | 397 (40) | 375 (43) | 327 (45) | 316 (43)  | 0.19      |
| IABP                   |             |      |      |      |      |           |
| All patients           | 192 (2.5)   | 56 (2.3) | 56 (2.8) | 47 (2.8) | 33 (2.2)  | 0.49      |
| HFpEF + HFmrEF         | 59 (1.4)    | 15 (1.0) | 19 (1.7) | 16 (1.7) | 9 (1.2)   | 0.36      |
| HFrEF                  | 133 (4.0)   | 41 (4.1) | 37 (4.2) | 31 (4.2) | 24 (3.2)  | 0.73      |
| PCPS                   |             |      |      |      |      |           |
| All patients           | 45 (0.6)    | 19 (0.8) | 10 (0.5) | 9 (0.5)  | 7 (0.5)   | 0.58      |
| HFpEF + HFmrEF         | 17 (0.4)    | 7 (0.5) | 4 (0.4) | 4 (0.5)  | 2 (0.2)   | 0.90      |
| HFrEF                  | 28 (0.8)    | 12 (1.2) | 6 (0.7) | 5 (0.7)  | 5 (0.7)   | 0.52      |
| In-hospital mortality  |             |      |      |      |      |           |
| All patients           | 567 (7.5)   | 183 (7.4) | 141 (7.1) | 122 (7.3) | 121 (8.2) | 0.62      |
| HFpEF + HFmrEF         | 291 (6.8)   | 101 (6.8) | 74 (6.6) | 65 (7.0) | 51 (6.9)  | 0.99      |
| HFrEF                  | 276 (8.3)   | 82 (8.2) | 67 (7.6) | 57 (7.8) | 70 (9.5)  | 0.53      |

HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IABP, intra-aortic balloon pump; IQR, interquartile range; IV, intravenous; NPPV, non-invasive positive pressure ventilation; PCPS, percutaneous cardiopulmonary support.

Values are presented as $n$ (%). In-hospital management and mortality were compared according to the IQRs of the lowest ambient temperature (IQR1 <5.5°C; IQR2 5.5–13.3°C; IQR3 13.3–19.7°C; and IQR4 >19.7°C).
In the HFrEF group, patients with high BNP values showed less increment in percent-incidence of AHF admission (P for interaction = 0.03). Further, HFrEF patients with ischaemic aetiology also showed a larger increment of percent-incidence of AHF admission (P for interaction = 0.048). The sensitivity analysis of the subdivided groups is shown in Table S3, indicating the increment of percent incidence of AHF admission was attenuated for younger patients (under 50 years) and for those with higher BNP (Quintile 5: over 1617 pg/mL).

The difference in the effect of temperature change on AHF admissions in relation to EF is shown in Figure 3B. HFrEF patients demonstrated the greatest incremental increases in the incidence of AHF, followed by HFmrEF and HFrEF patients [percent change (95% CI) 3.5 (3.0–4.0)% vs. 2.8 (2.2–3.5)% vs. 1.5 (1.0–2.0)% per −1°C, P < 0.001]. The association between percent-incidence of AHF admission and lowering ambient temperature was consistent in each HFpEF patients and in HFrEF patients irrespective of EF range.

The effect of ambient temperature on the in-hospital treatment and outcome

In-hospital treatment and mortality are described according to the IQRs of the lowest ambient temperature in Table 2. The overall in-hospital mortality rate was 7.5% and did not significantly change according to ambient temperature (P = 0.62). The patients’ use of inotropic medications was more frequent in the higher temperature range (P = 0.04), while vasodilator medication was most commonly used in the lower temperature range (P = 0.01).

Discussion

We explored the difference in the effect of ambient temperature on the incidence of AHF based on its phenotype. Lower ambient temperature was associated with increasing incidence of AHF, and this effect was more pronounced in the HFpEF + HFmrEF group than in the HFrEF group. In the sensitivity analysis, the decrease in the ambient temperature was associated with the greatest incremental increases in HFpEF, followed by HFmrEF and HFrEF patients. Moreover, hypertension was pathognomonic for AHF patients who were vulnerable to changes in ambient temperature.

The inverse association between AHF incidence and ambient temperature has been reported in several countries. In accordance with previous reports, the present study revealed a negative correlation between the lowest temperature and the AHF incidence in the metropolitan Tokyo area, which lies in a subtropical climate zone. The reproducibility of this association might support the fact that this effect was not limited to specific regions or climatic zones. Regarding prognosis, the effect of ambient temperature on the mortality of AHF patients has been controversial. We showed that in-hospital mortality did not significantly change according to temperature change, but there was a trend of higher mortality rates in the lowest and highest temperature range groups, which was consistent with previous reports. This trend could be related to the increase in inotropic medication use in the highest temperature range.

We also demonstrated that the effects of lowering ambient temperature on hospital admissions were enhanced in HFpEF patients compared with HFrEF patients, which persisted across all subgroups classified according to age, sex, and comorbidities including a history of hypertension. Previously, a higher rate of AHF admission has been reported for HFrEF patients with various triggers. Therefore, the effect of ambient temperature could be relatively attenuated in patients with lower EF. However, the extent of this effect did not show a linear change according to EF but was consistent in each HFpEF and HFrEF group, irrespective of EF range (50–60% and over 60% in HFpEF, and under 30% and 30–40% in HFrEF) (Figure 3B). Therefore, the enhanced effect of ambient temperature on HFpEF might not be merely explained by the severity of disease determined by EF, but rather reflect the difference in the pathophysiology between HFpEF and HFrEF.

Although various underlying factors contribute to the formation of HFpEF, the substantial role of microvascular and macrovascular dysfunction has been pointed out. Recent studies have proposed the involvement of coronary microvascular dysfunction in the pathogenesis of HFpEF. The effect of ambient temperature on vascular function has been reported previously: lowering in ambient temperature was associated with an impairment of vascular endothelial function and an increase in neural humoral factors, which could contribute to an increase in vascular resistance. Furthermore, these effects were amplified in patients with HF due to an impaired thermoregulatory system. It seems likely that the change in the microvascular environment induced by temperature change, which was basically related to the pathogenesis of HFpEF, was one possible cause of the vulnerability of HFpEF patients to low ambient temperatures. Interestingly, the present study demonstrated that HFrEF patients with ischaemic aetiology also showed an enhanced response to temperature change. This might support the hypothesis that AHF with cardiac dysfunction, accompanied by impairment of vascular function, might show an enhanced response to lowering ambient temperature. Further studies, including the assessment of vascular function, are needed to confirm this hypothesis.

In addition to micro-vessel dysfunction, abnormal function of systemic vessels was frequently observed in HFpEF. In the present study, a stronger effect of low ambient
temperature was observed in patients with sBP > 140 mmHg, despite little effect in patients with sBP < 100 mmHg. In addition, sBP could have a mediation effect on the relationship between temperature change and AHF admissions. Numerous studies have demonstrated that the low ambient temperature increases the sBP due to elevated systemic vascular resistance. The increase in vascular resistance and consequent afterload mismatch could contribute to the development of AHF, leading to an increase in hypertensive AHF patient admissions. In our study, patients with a history of hypertension were not found to be at greater risk for AHF due to ambient temperature changes. However, the daily hypertension management routines of these patients were not known and could not be considered. This factor could affect the variation of AHF admissions resulting from ambient temperature change and account for the difference between HFP EF and HFr EF patients. Regardless of a patient’s history of hypertension, attention should be paid to blood pressure in the management of patients at risk for AHF, especially in cold climates.

The elderly and female patients were more vulnerable to temperature change and demonstrated higher incremental increases in AHF admissions with lowering of ambient temperature in the present study. The higher prevalence of HFP EF in elderly and female patients may have contributed to the vulnerability of these patients. In addition, patients with higher BNP levels showed an attenuated response to ambient temperature change, and the contributing factor was uncertain in the present study. Patients presenting with higher BNP levels could have poorer baseline condition. In these patients, various triggers worsened HF, and the effect of temperature change could relatively be attenuated. In addition, patients with severe HF tend to be inactive. These patients would have fewer opportunities to be exposed to ambient climate, and the effect of ambient temperature change may be relatively attenuated. To further explore this issue, the analysis on behavioural patterns and exposure to ambient temperature might be necessary in the future.

Various triggers could contribute to worsening HF and might have effect on the association of AHF and climate condition. Lower ambient temperature is known to be associated with the onset of atrial fibrillation. However, the contribution of the tachyarrhythmia or bradyarrhythmia was unremarkable in the present study. In addition, infection could also cause an increase in AHF admissions during winters. The increase in AHF admissions with temperature change was not significantly different between the patients with higher and lower C-reactive protein levels, while the utility of C-reactive protein in the diagnosis of respiratory infection was limited. Further investigations are needed to reveal the mechanism underlying the increase in AHF admissions with lower ambient temperature.

Several limitations should be noted. First, there might be imprecision in the clinical assessment of EF. Patients with HFr EF showed an intermediate increase in AHF admissions caused by ambient temperature changes, compared with patients with HFP EF and HFr EF. This intermediate increase might not be solely attributed to HFr EF because the imprecision in measurement of EF for this subgroup could affect this result. Second, patients with missing data on EF (15.9%) were excluded. The characteristics of these patients were similar to the HFP EF patients (Table S6), and the percent change of AHF incidents with missing EF data resembled that of HFr EF [percent change (95% CI): 3.4 (2.8–4.0)]. Third, there might be selection biases because the registry was limited to data from the metropolitan Tokyo area. However, this regional data allowed the assessment of the effect of temperature change under the same climate conditions with detailed patient data. A multicentre cohort design could minimize the effect of selection biases. Finally, this is a retrospective study and has an intrinsic limitation due to its design. The rate of intravenous loop diuretic use was 81%, and misdiagnosis of HFP EF could be a concern. The usage rate of intravenous loop diuretic for hospitalized HFP EF patients was reported to be 67–81% in the nationwide registries of Japan. The current guidelines from the Japan Circulation Society recommend the use of vasodilators as the first-line treatment for AHF. In the present study, the major in-hospital treatments for HFP EF patients without intravenous loop diuretics were oral loop diuretics (59.6%) and isosorbide dinitrates (81.4%). Furthermore, in this population, the median value of BNP was 717 (324–1322) pg/mL, which was equivalent to the median BNP value of all patients [769 (434–1385) pg/mL]. Despite the above, there are still possibilities of missing records regarding the use of intravenous loop diuretics or the misdiagnosis of HFP EF, because of the retrospective design. In addition, causation cannot be inferred. We could not determine whether hypertension induced the worsening of HF or whether hypertension and AHF developed independently in patients who were vulnerable to temperature change. However, considering that intensive blood pressure control was reported to decrease AHF admissions, clinicians should recognize that elevated blood pressure could be a sign of worsening HF. The causal relationship among temperature change, sBP, and AHF admission should be investigated prospectively in the future studies.

In conclusion, this analysis of a population-based registry demonstrated heterogeneity in the effect of ambient temperature on AHF incidence. Patients with HFP EF showed a stronger response to the lowering of ambient temperature than those with HFr EF. In addition, hypertensive condition was pathognomonic for AHF in a cold climate. Information on the ambient temperature changes should be considered in routine care, particularly in HFP EF patients. Furthermore, careful attention should thus be given in the management of the blood pressure in cold climates for patients at risk for AHF.
Acknowledgements

All authors have made contribution to the study, and their roles were as follows: TJ, SK, and MY designed the study and constructed the first draft. TO and TJ conducted the statistical analysis. KH, KN, and MT supervised the work. All authors had access to the data and contributed to the acquisition and the interpretation of the data. All of the authors made comments and revisions to the final manuscript and approved it. The authors appreciate all members of the Tokyo CCU Network Scientific Committee and Ms Nobuko Yoshida (Tokyo CCU Network office) for data collection.

Conflict of interest

Dr Kohsaka reports investigator-initiated grant funding from Daiichi Sankyo and Novartis and personal fees from AstraZeneca and Bristol-Myers Squibb, outside the submitted work. Dr Shiraishi is affiliated with an endowed department by Nippon Shinyaku Co., Ltd. and reports personal fees from Otsuka Pharmaceutical, outside the submitted work. The remaining authors have no conflicts of interest to declare.

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Funding

This work was supported by the Tokyo Metropolitan Government, which had no role in the interpretation of results.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Meteorological background of Tokyo (2015–2016).
Table S2 Models for estimating daily admissions of AHF.
Table S3 Sensitivity analysis for the percent change of acute heart failure admissions according to subdivided groups.
Table S4 The estimation of the mediator effect of systolic blood pressure on the relationship between the temperature change and AHF admissions.
Table S5 The patient characteristics according to the interquartile ranges of the ambient lowest temperature.
Table S6 Characteristics of patients without LVEF data.
Figure S1 Trends in ambient temperature and the number of incidents of acute heart failure per day in Tokyo.
Figure S2 Forest plots comparing the percent change of acute heart failure admission for all patients.
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