

# openheart Impact of residence altitude on readmission in patients with heart failure

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## ABSTRACT

**Objective** Mountain districts normally have tougher geographic conditions than plain districts, which might worsen heart failure (HF) conditions in patients. Also, those places frequently are associated with social problems of ageing, underpopulation and fewer medical services, which might cause delay in detection of disease progression and require more admissions. We investigated the association of residence altitude with readmission in patients with HF.

**Methods** We followed 452 patients with HF to determine all-cause readmissions over a median of 1.1 years. The altitude of patient residences, population, proportion of the elderly and number of hospitals or clinics in a minor administrative district (Cho-Aza district) located at the residences were examined using data from the 2010 census and Google Maps.

**Results** All-cause readmissions were observed in 269 (60%) patients. The altitude of  $\geq 200$  m was significantly associated with readmissions (HR, 1.49; 95% CI 1.12 to 1.96;  $p=0.006$ ) after adjustment for physical and haemodynamic parameters, left ventricular ejection fraction, brain natriuretic peptide and components of the established score for predicting readmission for HF. Altitude was significantly associated with ageing, underpopulation, fewer hospitals or clinics and lower temperature (all  $p<0.01$ ), with an increased tendency for readmission during the winter season; however, it was not associated with patient clinical parameters.

**Conclusions** High altitude residence may be an important predictor for readmission in patients with HF. This relationship may be confounded by unfavourable sociogeographic conditions at higher altitudes.

## INTRODUCTION

Heart failure (HF) is a leading cause of hospital readmission in patients aged  $>65$  years.<sup>1</sup> Readmission rates still are increasing.<sup>2</sup> This poses significant problems, including prognosis, impaired quality of life and increased costs and resource use.<sup>1-4</sup> Also, ageing patients with HF are increasingly common in an ultra-ageing society, and the majority of them are frail and suffer from multiple chronic comorbidities.<sup>5-10</sup>

## Key questions

### What is already known about this subject?

- Heart failure (HF) readmissions are a common and serious problem of heterogeneous aetiology.
- Mountain districts normally have tougher geographic conditions than plains districts.
- Those places frequently are associated with ageing, underpopulation and fewer medical services.

### What does this study add?

- Residence at high altitudes may be an important risk factor for readmission in patients with HF.
- This relationship may be confounded by unfavourable sociogeographic conditions at higher altitudes.

### How might this impact on clinical practice?

- Clinician should recognise the residence of patients with HF as a risk factor for readmission.
- Policy makers should consider improvement of unfavourable social conditions of mountain districts.

These patients require readmissions due to worsening HF and other comorbidities.<sup>2</sup>

Geographically, Japan is known for its rugged, mountainous terrain; over 70% of the national land consists of mountains and hills, particularly in the rural areas. Mountain districts normally have steeper slopes, lower temperatures and greater temperature changes than the plains, which might worsen HF conditions in patients.<sup>11-13</sup> Also, those places frequently are associated with social problems of ageing, underpopulation and fewer medical services, which might cause delay in detection of disease progression and require more admissions.

Many readmissions for HF are predictable and, therefore, possibly preventable.<sup>1 14 15</sup> Recently, identifying risks in the environment following hospitalisation for HF has been studied for more appropriate prevention of readmission.<sup>16</sup> On these grounds, it is important for policy makers and clinicians to recognise the sociogeographic and clinical factors causing patients to be at highest risk



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for readmission.<sup>17</sup> Therefore, we investigated the association of altitude of the residence with readmission and its confounding factors in patients with HF.

## METHODS

### Study subjects

This is a retrospective cohort study. We evaluated patients enrolled from the Kitaishikai Hospital admission database, which consists of all admitted patients and their primary diagnosis code (International Classification of Diseases, 10th revision code (ICD-10)) related to the index admission. From this database, we identified 525 consecutive patients (age range, 30–90 years) admitted to Kitaishikai Hospital in Ozu City, from July 2006 to June 2014, with a primary diagnosis of congestive HF (ICD-10 codes, I500 congestive HF, I501 left ventricular failure, and I509 HF, unspecified). Ozu City is located in Ehime Prefecture on the western coast of Shikoku, in a rural area of Japan. Its population is small (approximately 35 000 people). Kitaishikai Hospital is a main hospital in Ozu City to back up general physicians, and most regular patients are usually admitted to this hospital. Furthermore, only Kitaishikai Hospital provides cardiology services in this medical district. Two cardiologists (KT and TM) independently checked each patient's medical record to confirm the diagnosis of HF. Any disagreement was resolved by a third cardiologist (TS). The definition of HF was as a combination of typical signs or symptoms and objective evidence of cardiac dysfunction (chest X-ray and echocardiography) in reference to the previous report.<sup>18</sup> The following patients were excluded because the reason of admission was not HF (n=73): coronary artery disease (n=29), followed by hospital transfer at the date of admission (n=9), renal failure (n=8), workup (n=5), lung disease (n=4), arrhythmia (n=4), depression (n=4), dehydration (n=4), cerebrovascular disease (n=3) and cancer (n=3). Finally, 452 patients were enrolled in the study.

### Clinical data

The clinical parameters at discharge (demographic variables, comorbidity and medical history, sociodemographic variables and vital signs) were collected by an investigator blinded to the findings using the medical records. Serum markers and left ventricular ejection fraction acquired closest to discharge were also assessed. B-type natriuretic peptide (BNP) at admission also was collected in addition to the data on BNP at discharge.

The conventional risk score to predict all-cause readmission of a patient with HF according to the study of Krumholz *et al* was also calculated.<sup>19</sup> The score assigned points according to four variables (0 and 4 indicating the lowest and highest, respectively). One point was added to each variable as follows: any admission during the previous year, history of HF or diabetes mellitus and serum creatinine >2.5 mg/dL at discharge. In our study,

the history of HF admission before the index admission was applied as 'history of HF'.

### Sociogeographic and climate data

The altitude of patients' residences was determined using Google Maps Elevation API (<https://developers.google.com/maps/documentation/javascript/elevation>). The population and proportion of the elderly (≥65 years and ≥75 years) in the minor administrative district (Cho-Aza district) located at the residence were assessed using data from the 2010 census (<http://www.stat.go.jp/english/index.html>). Median area of the Cho-Aza district was 3.8 km<sup>2</sup> (IQR, 1.6–8.7 km<sup>2</sup>). Google Maps (<https://maps.google.com/>) was used to measure the distance from the residence to Kitaishikai Hospital and to determine the number of hospitals or clinics in the Cho-Aza district (dental, paediatrics, obstetrics and gynaecology and ophthalmology clinics were excluded; online supplementary figure 1. Furthermore, average daily temperature from July 2006 to June 2014 in the major administrative district (Gun-City district) located at the residence was checked using data from the Japan Meteorological Agency (<http://www.jma.go.jp/jma/indexe.html>).

### Outcome

The primary endpoint included all-cause unplanned readmission after discharge. Only readmission data for Kitaishikai Hospital were analysed considering Kitaishikai Hospital characteristics. Two cardiologists (SI and MS) checked each medical record to confirm readmission. The secondary endpoint included HF-specific readmission assessed by a similar definition of inclusion criteria. Patients were censored at the time of each outcome or at the end of follow-up (31 July 2015).

Since Japan is located in the northern hemisphere, readmission from April to September was defined as readmission in the summer season and from October to March as readmission in the winter season.

### Statistical analysis

Data were missing from 0.8% of the records, except for BNP at discharge (11.5%). Missing BNP at discharge was imputed from propensity score models using parameters without missing data (age, sex, body mass index (BMI), systolic blood pressure, heart rate, BNP at admission, diabetes mellitus, haemoglobin and serum creatinine). Other continuous variables (<5%) were imputed using the corresponding mean value.

Continuous data are expressed as mean±SD, or as median ((IQR)) according to the distributions of the study parameters. Survival analysis was performed using Cox proportional hazard analysis. The simple association of study variables with readmissions was assessed in the univariate analysis. The associations between readmissions and each geographic parameter were evaluated after the adjustment of the following patient clinical parameters: age, sex, BMI, systolic blood pressure, heart rate, left ventricular ejection fraction, haemoglobin,

BNP at discharge and four components of the Krumholz score. Particularly, the associations between readmissions and residence altitude were assessed by adjusting sociogeographic parameters as well as the patient clinical parameters. Univariate linear regression analyses were used to confirm the associations between altitude and study parameters in the present cohort. For multiple comparisons, a one-way analysis of variance was used, followed by Bonferroni correction. Statistical analysis was performed using the Standard Statistical Software Package (SPSS) software V.20.0, and  $p < 0.05$  indicates statistical significance.

## RESULTS

### Patient characteristics

Table 1 summarises patient baseline clinical and geographic parameters. Median altitude of patient residences was 64 m. Median proportion of the population  $\geq 65$  years in the Cho-Aza district located at the residence was 35%. This proportion obviously was higher than the average percentage of the population  $\geq 65$  years in Japan in 2010 (23%). Median number of hospitals or clinics in that district was zero.

### Events

Follow-up data were available for all 452 patients with 269 (60%) all-cause readmissions over a median of 1.1 years (IQR 0.3–2.9 years). Of these readmitted patients, only 132 (49%) were readmitted because of worsening HF. The most common reason for readmission other than HF was lung disease (37 events, 14%), followed by kidney and urinary disease (20 events, 7%).

The secondary outcome, HF-specific readmission, was observed in 145 (32%) patients over a median of 2.5 years (IQR 0.9–4.8 years).

### Association of residence altitude with readmissions

Altitude of patient residences (per 25 m) was significantly associated with all-cause readmission (HR 1.02; 95% CI, 1.00 to 1.05;  $p = 0.04$ ) and HF-specific readmission (HR 1.04; 95% CI 1.01 to 1.07;  $p = 0.01$ ).

Table 2 shows associations of geographic and climate parameters with readmissions after adjustment of patient clinical parameters. Residence altitude was associated with both outcomes. Particularly, the associations between altitude  $\geq 200$  m and readmissions were significant. Also, all-cause readmission tended to be associated with ageing and underpopulation in the vicinity of the residence.

### Factors associated with residence altitude

Table 3 shows the associations of residence altitude with study parameters. The altitude was significantly associated with remoteness from the hospital, ageing, underpopulation, fewer hospitals or clinics, lower temperature and greater temperature difference in the neighbourhood of the residence. Also, altitude was associated with winter season of readmission (figure 1). However, it was not associated with patient clinical parameters.

**Table 1** Patient characteristics

Variable	Overall (n=452)
Age (years)	81 (74–85)
Male sex, n (%)	240 (53)
Body mass index (kg/m <sup>2</sup> )	21.9±4.0
Systolic blood pressure (mm Hg)	113 (102–126)
Heart rate (per min)	66 (60–76)
Admissions in past year, n (%)	115 (25)
First admission due to heart failure	296 (66)
Diabetes, n (%)	124 (27)
Haemoglobin (g/L)	11.7 (10.2–13.0)
B-type natriuretic peptide at admission (pg/mL)	570 (308–1121)
B-type natriuretic peptide at discharge (pg/mL)	220 (112–423)
Creatinine (mg/dL)	1.0 (0.8–1.4)
Creatinine $\geq 2.5$ , n (%)	26 (6)
Left ventricular ejection fraction (%)	51 (41–62)
Krumholz score	1 (0–2)
Socioeconomic variables	
Living alone, n (%)	80 (18)
Low income*, n (%)	42 (9)
Number of housemates	1 (1–3)
Geographic and climate variables	
Altitude of patients' residence (m)	64 (15–188)
Altitude $\geq 200$ m of patients' residence, n (%)	100 (22)
Distance from patients' residence to hospital† (km)	16 (7–24)
Population‡ (persons)	647 (284–1863)
Proportion of the population $\geq 65$ years‡ (%)	35 (28–42)
Proportion of the population $\geq 75$ years‡ (%)	20 (16–25)
Number of hospital or clinics‡ (%)	0 (0–2)
Mean temperature in a day§ (°C)	15.7±0.3
Maximum daily temperature§ (°C)	21.0±0.9
Minimum daily temperature§ (°C)	11.5±0.8
Difference of daily temperature§ (°C)	9.5±1.5

Data are expressed as mean±SD, median (IQR) or number (percentage).

\*Patients who were certified as a resident tax exemption.

†Kitaishikai Hospital.

‡In the minor administrative district (Cho-Aza district) located at patients' residence.

§Average temperature in a day from July 2006 to June 2014 in the major administrative district (Gun-City district) located at patients' residence.

Accordingly, the associations between the residence altitude and readmission were reconfirmed by adjusting using patient clinical parameters (age, sex, BNP at discharge, hospitalisation in the prior year, history of HF admission, diabetes and creatinine  $> 2.5$  mg/dL) and sociogeographic variables (distance from patients' residence to hospital, population, proportion of the population  $\geq 75$  years, number of hospital or clinics and mean

**Table 2** Associations of geographic and climate parameters with outcomes after adjustment of patient clinical parameters

Variable	All-cause readmission HR (95% CI), p values	HF-specific readmission HR (95% CI), p values
Altitude of patients' residence (per 25 m)	1.03 (1.00 to 1.05), p=0.02	1.04 (1.01 to 1.07), p=0.02
Altitude of patients' residence $\geq$ 200 m	1.49 (1.12 to 1.96), p=0.006	1.97 (1.37 to 2.83), p<0.001
Distance from patients' residence to hospital* (per 1 km)	0.99 (0.98 to 1.00), p=0.23	1.00 (0.98 to 1.01), p=0.76
Population† (per 100 persons)	0.98 (0.97 to 1.00), p=0.009	0.99 (0.97 to 1.00), p=0.11
Proportion of the population $\geq$ 75 years† (per 1%)	1.02 (1.00 to 1.03), p=0.04	1.01 (0.99 to 1.04), p=0.45
Number of hospital or clinics†	0.98 (0.91 to 1.05), p=0.54	0.98 (0.90 to 1.08), p=0.69
Mean temperature in a day‡ (per 1°C)	0.97 (0.64 to 1.46), p=0.87	0.84 (0.48 to 1.47), p=0.53
Difference of temperature in a day‡ (per 1°C)	1.01 (0.93 to 1.10), p=0.74	0.94 (0.85 to 1.04), p=0.23

All associations of study variables with outcomes were adjusted by age, sex, BMI, systolic blood pressure, heart rate, left ventricular ejection fraction, haemoglobin, BNP at discharge, hospitalisation in the prior year, history of HF admission, diabetes and creatinine  $>2.5$  mg/dL. P<0.008, significant based on Bonferroni correction.

\*Kitaishikai Hospital.

†In the minor administrative district (Cho-Aza district) located at patients' residence.

‡Average daily temperature from July 2006 to June 2014 in the major administrative district (Gun-City district) located at patients' residence. BMI, body mass index;BNP, B-type natriureticpeptide;HF, heart failure.

**Table 3** Associations of residence altitude (per 25 m) with study parameters

Variables	$\beta$	95% CI	Standardised $\beta$	P values
Age (per 1 year)	0.03	-0.02 to 0.07	0.05	0.30
Male sex	-0.43	-1.33 to 0.47	-0.04	0.35
Haemoglobin (per 1 g/L)	0.05	-0.18 to 0.28	0.02	0.66
BNP at discharge (per 100 pg/mL)	0.01	-0.12 to 0.15	0.01	0.87
Left ventricular ejection fraction (per 5%)	0.05	-0.11 to 0.21	0.03	0.51
Krumholz score	0.02	-0.49 to 0.53	0.01	0.94
Living alone	-0.50	-1.58 to 0.57	-0.04	0.36
Low income*	0.32	-0.75 to 1.39	0.03	0.55
Number of housemates (per one person)	-0.08	-0.37 to 0.21	-0.03	0.59
Distance from patients' residence to hospital† (per 10 km)	1.31	0.94 to 1.67	0.32	<0.01
Population‡(per 100 persons)	-0.21	-0.24 to -0.17	-0.45	<0.01
Proportion of the population $\geq$ 75 years‡ (per 1%)	0.34	0.29 to 0.39	0.54	<0.01
Number of hospital or clinics‡	-0.99	-1.21 to -0.77	-0.39	<0.01
Mean temperature in a day§ (per 1°C)	-5.05	-6.47 to -3.63	-0.31	<0.01
Difference of temperature in a day§ (per 1°C)	0.58	0.28 to 0.88	0.18	<0.01

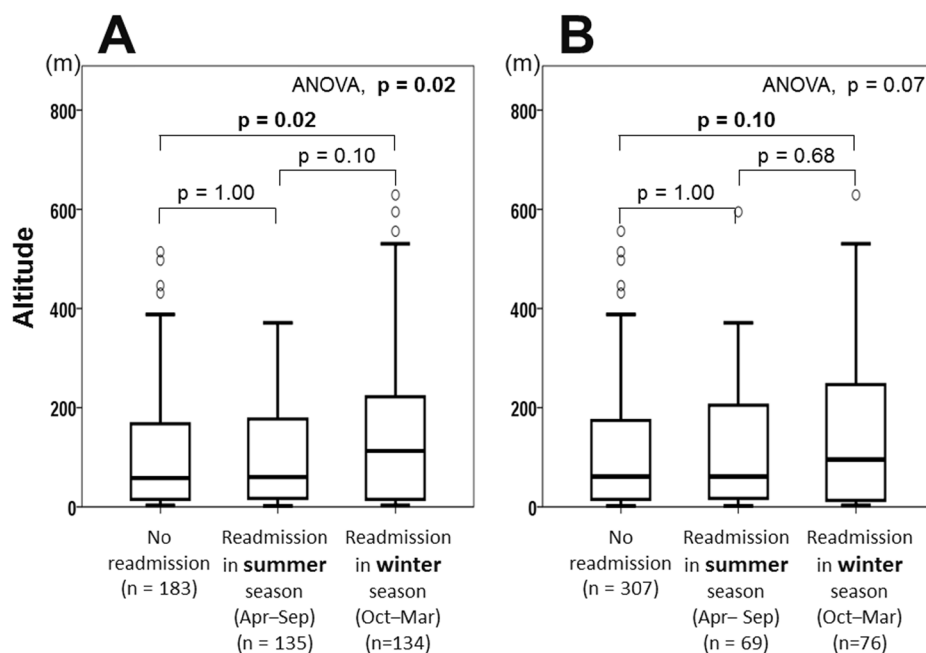
\*Patients who were certified as a resident tax exemption.

†Kitaishikai Hospital.

‡In the minor administrative district (Cho-Aza district) located at patients' residence.

§Average temperature in a day from July 2006 to June 2014 in the major administrative district (Gun-City district) located at patients' residence.

BNP, B-type natriuretic peptide.



**Figure 1** Association of residence altitude and season of readmission ((A): all-cause readmission; (B): heart failure-specific readmission). ANOVA, analysis of variance.

temperature in a day). As a result, HF-specific readmission was still strongly associated with residence altitude (per 25 m) (HR 1.04; 95% CI 1.00 to 1.09;  $p=0.03$ ), but the association between all-cause readmission with the altitude was further weakened (HR 1.02; 95% CI 0.99 to 1.05;  $p=0.19$ ).

## DISCUSSION

We demonstrated that residence altitude, particularly HF-specific readmission, could be a risk factor for readmission in patients with HF. Also, the relationship might be confounded by the unfavourable sociogeographic conditions at higher altitudes.

### Mechanism of the association between high altitude and readmissions

Nearly 70% of Japan is covered with mountains, more in rural areas, that have relatively steep slopes, low temperatures and large temperature changes even though they are not so high above sea level. These geographical disadvantages are frequently hard, particularly for elderly people and those with HF.<sup>11-13</sup> In addition, the mountain districts have social disadvantages, such as ageing, underpopulation and limited healthcare services, which might lead to delay in detection of worsening conditions and finally admission.

In fact, in our study, high altitude was significantly associated with unfavourable social and climate conditions as expected. Also, the association between all-cause readmission and residence altitude after adjusting for patient clinical conditions was further weakened after adding

the adjustment of sociogeographic parameters. These results could suggest that unfavourable sociogeographic conditions represented by residence altitude could be an important risk factor for readmission in patients with HF.

The cause of strong association between residence altitude and HF-specific readmission after adjustment with clinical and sociogeographic parameters was unknown but might be influenced by unmeasured confounder such as the steepness of slope.

Interestingly, the second and third most frequent causes of all-cause readmission were lung and renal diseases. These diseases could easily worsen during a relatively short period, particularly in elderly people. Therefore, their early detection is important. Possibly, the results of our study might partly explain the delay in detection at a high altitude area.

Several articles have reported the beneficial effects of high altitude exposure for improving anaemia and lung and heart function in elderly patients.<sup>20-22</sup> However, this type of high altitude generally is considered >2500 m above sea level.<sup>21</sup> In our study, left ventricular ejection fraction and haemoglobin were not associated with altitude. Because the present target places were not so high, altitude might be more associated with unfavourable sociogeographic condition rather than its beneficial effects.

### Associations between other sociogeographic and climate parameters and readmissions

In the present study, remoteness from the hospital, fewer healthcare services and the parameters regarding

temperature were not significantly associated with readmissions. The distance from the residence to the primary hospital was relatively close compared with distances noted in Western countries. Also, the study location included relatively warm and comfortable places, even at high altitudes. These reasons might explain the difference in our results from those of prior studies.<sup>13 17</sup> However, several articles have reported that remoteness was not necessarily associated with adverse outcomes, which was compatible with our results.<sup>23 24</sup>

### Clinical implication

Our study demonstrated that high altitude places in rural Japan were sociogeographically deprived places, which could worsen the conditions in patients with HF and cause readmissions. This information would be important especially for policy makers and hospital staff.

Because medical resources are limited, probably one solution would be to expand the monitoring system for patients using phones and information and communication technology.<sup>25 26</sup> Obviously, regular home visits by doctors and medical staff would be efficient, but preparation of financial support, such as long-term care insurance, would be crucial to take this service fairly.<sup>27</sup> Furthermore, enlightenment of residents regarding the importance of constructing the cooperation system in the neighbourhood would be effective.

### Study limitations

Our data should be interpreted according to the study's limitations. First, geographic bias may exist, and generalisation might be difficult because this is a single-centre study. However, high altitude places in our study represent poor sociogeographic areas. Therefore, our results may be reproduced in a location with a similar environment. Nonetheless, a much larger multicentre study is essential to confirm our results. Second, this retrospective analysis may have been biased because of potential unmeasured confounders such as steepness of slope, although we tried to correct the confounders regarding altitude. Finally, although most regular patients should be admitted to Kitaishikai Hospital, some might present to other hospitals. However, the possibility would be small considering the circumstances of Kitaishikai Hospital.

### CONCLUSIONS

We demonstrated that altitude of the residence could be a risk factor for readmission, particularly HF-specific readmission, in patients with HF in rural Japan. Additionally, this relationship might be confounded by the unfavourable sociogeographic conditions at higher altitudes. However, geographic bias may exist; therefore, a larger multicentre study should be warranted to confirm our results.

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**Contributors** MS designed the protocol and extracted and analysed the data, conducted the statistical analysis and drafted and revised the draft paper. MY, MO, ET, TM and KT extracted data and cleaned the data. SI contributed to conception and extracted data and revised the draft paper. TS revised the draft paper. All authors had full access to the data and are guarantors for the study.

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