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ORIGINAL ARTICLE

Association of Low Body Mass Index With In-Hospital Cardiac Arrest in Patients With Cerebro- and Cardiovascular Disease
— From the JROAD-DPC Database —

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Background: Although body mass index (BMI) is a simple marker of in-hospital cardiac arrest (IHCA) in patients with cerebro- and cardiovascular disease, the association between BMI on admission and the incidence of IHCA is still controversial. In this study, Japanese patients with cerebro- and cardiovascular disease were investigated for the association between BMI on admission and the incidence of IHCA.

Methods and Results: This was a retrospective study from the Japanese Registry Of All cardiac and vascular Diseases-Diagnosis Procedure Combination (JROAD-DPC), a large-scale nationwide claims-based database, using data from between 2012 and 2021. From among all 10,923,676 cases, 7,571,826 patients who were hospitalized for cerebro- or cardiovascular disease were investigated. BMI was classified as underweight (<18.5 kg/m²), normal and under ideal (18.5–22 kg/m²), normal and over ideal (22–25 kg/m²), or obese (≥25.0 kg/m²). The average age, ratio of males, and average BMI were 71.6±12.8 years, 63.4%, and 23.3±3.7 kg/m², respectively. IHCA occurred in 270,380 cases (3.57%). In a Cox regression analysis according to BMI group, the underweight group showed significantly higher hazard risk for the incidence of IHCA after adjusting cofounding factors, both in all patients and a subgroup analysis according to the patient's age generation.

Conclusions: Underweight, rather than obesity, might be a risk factor for IHCA in an aging society.

Key Words: Aging society; Body mass index; In-hospital cardiac arrest

Although rare, in-hospital cardiac arrest (IHCA) is a sudden and crucial event during hospitalization.[1] It is associated with a high mortality rate and high medical expenses.[1] Although the incidence of IHCA should be reported, especially for high-risk patients such as those with cerebro- and cardiovascular diseases,[2] there has been little progress in this area. In particular, despite several studies of IHCA, such as ECG monitoring,[3] therapeutic hypothermia,[4] drug usage,[5] hospital-level variation,[6] and COVID-19 infection,[7] there are few reports on the effect of these interventions on the incidence of IHCA.[2,8] Cerebro- and cardiovascular diseases were responsible for 23.2% of all deaths in Japan in 2018, and legislation for the promotion of measures against these diseases has been enacted.[9] Therefore, more studies of the incidence of IHCA among patients with cerebro- and cardiovascular diseases are needed.

Body mass index (BMI) is a measure of various physical conditions,[10] being body weight/height*height. Overweight reflects obesity and metabolic syndrome, and predicts cardiovascular death.[11–13] Underweight reflects frailty and sarcopenia, and also predicts cardiovascular death.[14–17] Therefore, BMI has been reported to have a J-shaped or U-shaped association with death.[18–20] In addition, country, race, socioeconomic level, and aging of society also affect BMI.[10,21] As mentioned, the association between BMI and death is paradoxical. Especially in an aging society, that asscociation should be gradually changing,[22] but the Japanese population is aging rapidly,[23] so it is important to under-

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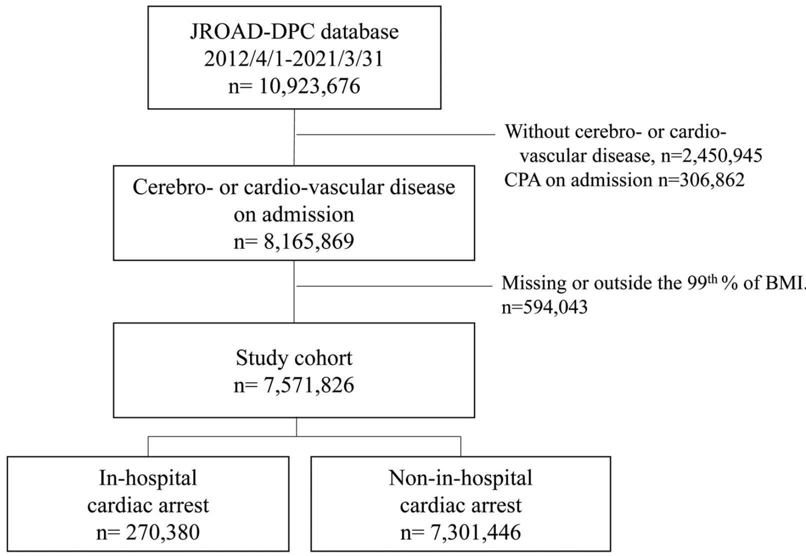


Figure 1. Study profile. From among a total of 10,923,676 cases, data for 8,165,869 patients who were admitted with cerebro- or cardiovascular disease and who did not have cardiopulmonary arrest (CPA) on admission were extracted. We omitted 594,043 cases in which body mass index (BMI) was outside the 99th percentile. The remaining 7,571,826 study cases included 270,380 IHCA cases. JROAD-DPC. Japanese Registry Of All cardiac and vascular Diseases-Diagnosis Procedure Combination.

stand the association between BMI and death under these conditions. In this study, we investigated the association between BMI on admission and the incidence of IHCA in Japan over the past 10 years.

Methods

Study Design

The study was performed in accordance with the Declaration of Helsinki and approved by the Independent Review Board of Fukuoka University (U20-597). From among 10,923,676 cases registered in the Japanese Registry Of All cardiac and vascular Diseases-Diagnosis Procedure Combination (JROAD-DPC), a large-scale nationwide claims-based database, from 2012 to 2021, we included 8,165,869 cases of patients hospitalized with cerebro- or cardiovascular disease. Cerebro- and cardiovascular diseases were identified by their International Classification of Diseases 10th Revision (ICD-10) codes on admission (**Supplementary Table 1**). We excluded 306,862 cases of cardiopulmonary arrest on admission and 594,042 cases for which BMI data were missing or outside the 99th percentiles (15.2–35.2 kg/m^2), because in some cases the data on height or body weight may not have been registered or registered incorrectly in the database. In particular, for emergency cases, there may not have been enough time to measure body weight on admission due to a need for emergency operation or catheter therapy. From among the remaining 7,571,826 cases, 270,380 IHCA cases were included. **Figure 1** shows the case selection criteria. We investigated baseline characteristics, medications, hospitalization days, cost, and prognosis during admission. The risk of IHCA was analyzed according to BMI groups. We divided BMI into 4 groups: underweight (<18.5 kg/m^2), normal and under ideal (18.5–22 kg/m^2), normal and over ideal (22–25 kg/m^2), and obese (≥25.0 kg/m^2) groups according to the definition.[24,25] We divided the cases by age into 4 generation groups: <64 years, 65–72 years, 73–80 years, and ≥81 years according to quartiles. We then performed a subgroup analysis for the risk of IHCA by BMI group by generation.

JROAD-DPC

The Japanese Circulation Society developed the nationwide JROAD-DPC database in 2012, with individual informed consent was obtained via the opt-out principle.[26] In 2021, DPC data from 1,243 institutes were registered. Race and ethnicity are not recorded, but almost all patients would be Japanese. The JROAD-DPC database includes age, sex, height, body weight, Brinkman index, admission conditions such as emergency or not, Charlson score, primary disease on admission, comorbidities, medications, treatment, hospitalization days, cost, and prognosis during admission.[26] Smoking was defined as a Brinkman index >0. In this study, we could not distinguish between current and past smoking. Details of the Charlson score are shown in **Supplementary Table 2**.

Outcomes

IHCA was defined as in-hospital death, cardiac massage, or open cardiac massage during admission and identified by the ICD-10 code at admission-precipitating diagnosis. Days of hospitalization were calculated from the date of admission to the date of IHCA, which was the earliest date of in-hospital death, cardiac massage, or open cardiac massage. Hospitalization days and costs, including direct costs, fees for service, and bundled payments, were also investigated.

Statistical Analysis

Continuous variables followed a normal distribution and are expressed as a mean±standard deviation, and differences between groups were compared using Student's t-test. Categorical variables are expressed as number (%), and differences between groups were compared by a chi-square analysis. IHCA events are shown as Kaplan-Meier survival estimates. Multilevel mixed-effect Cox regression analyses, using institution as a random intercept, were performed for hazard ratios to compare the incidence of IHCA in the 4 BMI groups, adjusted by age, sex, smoking,

Table 1. Baseline Characteristics of the IHCA and Non-IHCA Groups

Variables	All (n=7,571,826)	IHCA (n=270,380)	Non-IHCA (n=7,301,446)	P value
Age, years	71.6±12.8	79.0±12.4	71.4±12.8	<0.001
Male, n (%)	4,798,377 (63.4)	148,279 (54.8)	4,650,098 (63.7)	<0.001
BMI, kg/m²	23.3±3.7	21.8±3.7	23.4±3.6	<0.001
Smoking, n (%)	3,636,003 (48.0)	111,573 (41.3)	3,524,430 (48.3)	<0.001
Comorbidities				
Hypertension, n (%)	3,859,030 (51.0)	91,743 (33.9)	3,767,287 (51.6)	<0.001
Diabetes mellitus, n (%)	2,021,594 (26.7)	51,635 (19.1)	1,969,959 (27.0)	<0.001
Dyslipidemia, n (%)	2,661,773 (35.2)	31,194 (11.5)	2,630,579 (36.0)	<0.001
Administration by ambulance, n (%)	1,690,065 (22.3)	178,635 (66.1)	1,522,430 (20.7)	<0.001
Charlson score, points	1.67±1.40	2.28±1.73	1.65±1.38	<0.001
Medications				
RAAS, n (%)	2,662,475 (35.2)	64,103 (23.8)	2,598,372 (35.6)	<0.001
CCB, n (%)	2,774,161 (36.7)	103,772 (38.4)	2,670,389 (36.6)	<0.001
β-blocker, n (%)	2,457,406 (32.5)	84,802 (31.4)	2,372,604 (32.5)	<0.001
Diuretics, n (%)	2,159,274 (28.6)	146,107 (54.1)	2,013,167 (27.6)	<0.001
Antiplatelet, n (%)	3,246,787 (42.9)	84,237 (31.2)	3,162,550 (43.4)	<0.001
Anticoagulant, n (%)	6,048,271 (80.0)	159,732 (59.2)	5,888,539 (80.7)	<0.001
Statin, n (%)	2,457,585 (32.5)	48,544 (18.0)	2,409,041 (33.0)	<0.001

Data on medications were missing in 7,738cases. P value shows the comparison between IHCA group and Non-IHCA groups. BMI, body mass index; CCB, calcium channel blocker; IHCA, in-hospital cardiac arrest; RAAS, renin-angiotensin-aldosterone system.

Table 2. ICD-10 Codes of Top 10 Primary Diseases on Admission

Variables	All (n=7,571,826)	IHCA (n=270,380)	Non-IHCA (n=7,301,446)	P value
I20 Angina pectoris, n (%)	1,768,186 (23.4)	5,112 (1.9)	1,763,074 (24.1)	<0.001
I50 Heart failure, n (%)	1,049,178 (13.9)	88,895 (32.9)	960,283 (13.2)	<0.001
I63 Cerebral infarction, n (%)	668,091 (8.8)	29,901 (11.1)	638,190 (8.7)	<0.001
I25 Chronic ischemic heart disease, n (%)	500,836 (6.6)	1,784 (0.7)	499,052 (6.8)	<0.001
I48 Atrial fibrillation and flutter, n (%)	436,479 (5.8)	2,203 (0.8)	434,276 (5.9)	<0.001
I21 Acute myocardial infarction, n (%)	332,586 (4.4)	30,008 (11.1)	302,578 (4.1)	<0.001
I71 Aortic aneurysm and dissection, n (%)	317,691 (4.2)	22,189 (8.2)	295,502 (4.0)	<0.001
I70 Atherosclerosis, n (%)	284,283 (3.8)	4,250 (1.6)	280,033 (3.8)	<0.001
T82 Complications of cardiac and vascular prosthetic devices, implants and grafts, n (%)	229,739 (3.0)	1,916 (0.7)	227,823 (3.1)	<0.001
I61 Intracerebral hemorrhage, n (%)	211,456 (2.8)	29,280 (10.8)	182,176 (2.5)	<0.001

Primary disease on admission was picked up from ICD-10 code at trigger disease on admission. P value shows the comparison between IHCA and Non-IHCA groups. IHCA, in-hospital cardiac arrest.

admission by ambulance, hypertension (HT), diabetes mellitus (DM), dyslipidemia (DLP) and the Charlson comorbidity index. The SAS Software Package (Ver. 9.4, SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis. STATA (Ver.17.0, College Station, TX, USA) was also used for Kaplan-Meier survival estimates. Statistical significance was set at $P<0.05$.

Results

Baseline Characteristics of IHCA and Non-IHCA Cases

Baseline characteristics are shown in **Table 1**. For all cases, the average age was 71.6±12.8 years. In Japan, the age on admission for cerebro- or cardiovascular diseases is high. The ratio of males was 63.4% (n=4,798,377), and the average BMI was 23.3±3.7 kg/m². The IHCA group were older, and had a lower percentage of males, and a lower BMI compared with the Non-IHCA group. The IHCA group had low percentages of smoking, hypertension, diabetes mellitus, and dyslipidemia. Both the Charlson score, which is an index of short-term death, and the percentage of patients who were admitted by ambulance were high in the IHCA group. With regard to medications, the IHCA group had lower percentages of renin-angiotensin-aldosterone system agents, β-blockers, antiplatelets, anticoagulants, and statins, and higher percentages of calcium-channel blockers (CCBs) and diuretics.

Primary Diseases on Admission

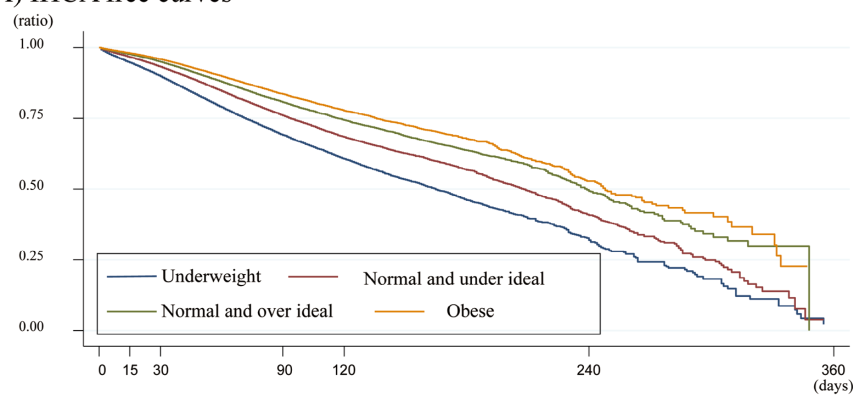
The top 10 primary diseases on admission according to the ICD10 code are shown in **Table 2**. The top 3 diseases overall and in the Non-IHCA group were angina pectoris, heart

Table 3. Outcomes in the IHCA and Non-IHCA Groups

Variables	All (n=7,571,826)	IHCA (n=270,380)	Non-IHCA (n=7,301,446)	P value
Hospitalization days	13.0±17.2	21.3±28.8	12.7±16.6	<0.001
Cost				
Direct cost, ×10³ yen	1,285±1,560	1,998±2,856	1,258±1,483	<0.001
Fee for service, ×10³ yen	854±1,296	1,286±2,325	838±1,239	<0.001
Bundled payment, ×10³ yen	430±477	711±899	420±451	<0.001
Death within 1 day, n (%)	31,509 (0.42)	31,509 (11.7)	0	<0.001
Death within 7 days, n (%)	111,202 (1.47)	111,202 (41.1)	0	<0.001
Death within 30 days, n (%)	198,432 (2.62)	198,432 (73.4)	0	<0.001
Total deaths, n (%)	251,995 (3.33)	251,995 (93.2)	0	<0.001

Data on costs was missing for 27,490 cases. P value shows the comparison between IHCA and Non-IHCA groups. IHCA, in-hospital cardiac arrest.

(A) IHCA free curves



Number at risk	0	15	30	90	120	240	360
Underweight	660552	281944	117818	10708	4448	147	0
Normal and under ideal	2172568	709922	261386	22056	9466	311	0
Normal and over ideal	2462059	648123	213765	17038	7585	230	0
Obese	2276647	544705	171001	13035	5713	167	0

(B) Cox regression analyses

	Unadjusted			Adjusted		
	HR	95% CI	p value	HR	95% CI	p value
Underweight						
Normal and under ideal	0.672	0.665-0.680	<0.001	0.808	0.800-0.817	<0.001
Normal and over ideal	0.495	0.490-0.501	<0.001	0.713	0.705-0.721	<0.001
Obese	0.411	0.406-0.417	<0.001	0.719	0.710-0.729	<0.001

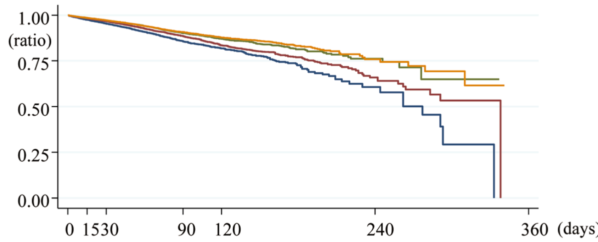
Figure 2. IHCA-free curves (**A**) and Cox regression analysis for IHCA (**B**) according to body mass index (BMI). Blue, red, green, and orange bars indicate the underweight, normal and under ideal, normal and over ideal, and obese BMI groups, respectively. Cox regression analysis was performed while adjusting for age, sex, smoking, admission by ambulance, hypertension, diabetes mellitus, dyslipidemia, and the Charlson score. CI, confidence interval; IHCA, in-hospital cardiac arrest; HR, hazard ratio.

failure, and cerebral infarction. The top 3 diseases in the IHCA group were heart failure, acute myocardial infarction, and cerebral infarction. The percentages of aortic aneurysm and dissection, and intracerebral hemorrhage were also high in the IHCA group.

Outcomes in IHCA and Non-IHCA Cases

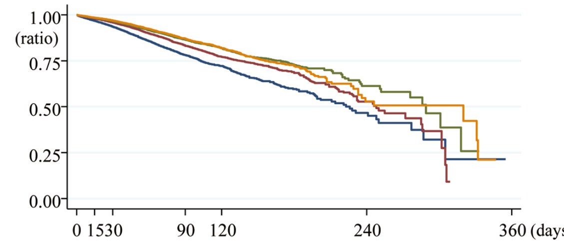
In the IHCA group, the average number of days until IHCA was 17.5±26.9 (**Table 3**); in 198,432 cases (73.4%), the patient died within 30 days and in 251,995 cases (93.2%) death occurred during admission. The number of days of hospitalization in the IHCA group was greater than that in the Non-IHCA group (IHCA group: 21.3±28.8 days, vs. Non-IHCA group: 12.7±16.6 days, P<0.001). The direct cost in the IHCA group was greater than that in the Non-IHCA group (IHCA: 1,998±2,856 ×10³ yen, vs. Non-IHCA: 1,258±1,483 ×10³ yen, P<0.001).

(A) 1st Q (Age <64)



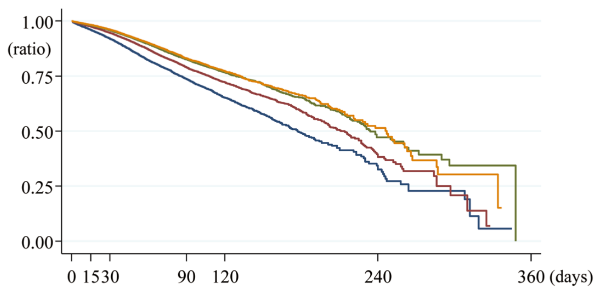
Cox regression analysis	HR	95% CI	p value
Underweight			
Normal and under ideal	0.815	0.783-0.850	<0.001
Normal and over ideal	0.779	0.748-0.812	<0.001
Obese	0.858	0.824-0.894	<0.001

(B) 2nd Q (65 ≤ Age <73)



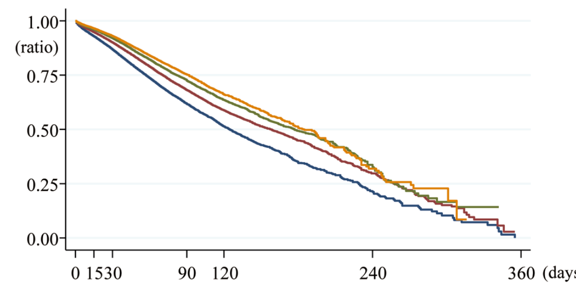
Cox regression analysis	HR	95% CI	p value
Underweight			
Normal and under ideal	0.764	0.739-0.790	<0.001
Normal and over ideal	0.694	0.671-0.718	<0.001
Obese	0.702	0.678-0.728	<0.001

(C) 3rd Q (73 ≤ Age <81)



Cox regression analysis	HR	95% CI	p value
Underweight			
Normal and under ideal	0.771	0.753-0.790	<0.001
Normal and over ideal	0.657	0.641-0.674	<0.001
Obese	0.657	0.639-0.675	<0.001

(D) 4th Q (81 ≤ Age)



Cox regression analysis	HR	95% CI	p value
Underweight			
Normal and under ideal	0.842	0.831-0.854	<0.001
Normal and over ideal	0.757	0.746-0.769	<0.001
Obese	0.723	0.710-0.737	<0.001

Figure 3. Age quartile subgroup analyses: <64 years (**A**), 65–72 years (**B**), 73–80 years (**C**), and ≥81 years (**D**). IHCA-free curves and Cox regression analysis for IHCA according to body mass index (BMI) are shown. Blue, red, green, and orange bars indicate the underweight, normal and under ideal, normal and over ideal, and obese BMI groups, respectively. Cox regression analysis was performed after adjusting for age, sex, smoking, admission by ambulance, hypertension, diabetes mellitus, dyslipidemia, and the Charlson score. CI, confidence interval; IHCA, in-hospital cardiac arrest; HR, hazard ratio.

Association With BMI on Admission and the Incidence of IHCA

The incidence of IHCA according to the 4 BMI groups is shown in **Figure 2**. The JROAD database registered DPC data by fiscal year and more than 1 year record did not include in this study. In a multivariate Cox regression analysis, the underweight group showed significantly higher hazard risk for the incidence of IHCA among the 4 BMI groups. We performed subgroup analyses to reveal the association between BMI on admission and the incidence of IHCA according to generation (**Figure 3**). The unadjusted results of a multivariate Cox regression analysis in these subgroup analyses are shown in **Supplementary Table 3**. Underweight groups showed significantly higher hazard risk for the incidence of IHCA in all generation subgroup analyses.

Discussion

In this study, the underweight group showed the highest hazard ratio for IHCA among the 4 BMI groups of patients with cerebro- and cardiovascular diseases in Japan in recent times. Patients with IHCA required more days of hospitalization and incurred a greater cost.

The Japanese population is the oldest in the world and continues to age rapidly.[23] The Japanese Cabinet Office reported that the percentage of the population aged ≥65 exceeded 28.8% in 2020.[27] In Japan, those aged 85–89 years accounted for the most deaths in 2020, whereas in 1955 the population aged 70–74 years accounted for the most deaths.[28] In this aging society, the percentage of older adults who require hospitalization is high and IHCA is a social problem.

The JROAD-DPC is a nationwide database[29] and has been used for research into IHCA.[30,31] In the present study, the average age on admission for cerebro- and cardiovascular diseases was 71.6±12.8 years. Thus, most cases were older adult patients, which may account for our subgroup analyses of the association between IHCA and BMI according to generation producing the same results of each age group. Over the past 10 years, 270,380 IHCA cases (3.57%) from among 7,571,826 cases of cerebro- and cardiovascular diseases were registered in JROAD-DPC. This high percentage of IHCA could be due to the JROAD-DPC database including data from facilities that offer long-term care, because the JROAD-DPC registry recruits data nationwide from university hospitals, national and public hospitals, and general hospitals. Thus, this result reflects the current situation in Japan. Overall, 763,970 cases (10.1%) were hospitalized for at least 30 days. Some patients remaining hospital until the end of life might affect our results, but we could not determine this from the JROAD-DPC database and may be the reason why the IHCA-free curves goes to nearly 0 over 360 days. Along with the percentage of IHCA, this long hospitalization could have been affected by data from long-term care facilities.

In this study, being underweight showed the highest hazard ratio for IHCA among the 4 BMI groups. Underweight reflects frailty and sarcopenia and predicts cardiovascular death.[14–17] It is also a risk factor for cardiovascular disease, in addition to metabolic risk factors.[32] In an aging society, both frailty and sarcopenia would strongly affect the outcome of IHCA. Cardiac cachexia is a common complication for heart failure patients and has a poor prognosis.[33] It influences sympathetic nerve activity, cortisol, the renin-aldesterone system, and levels of inflammatory cytokines.[33] Age-related atrophy is associated with oxidative stress.[34] Mitochondrial deoxyribonucleic acid mutation has been suggested to be related to aging and sarcopenia.[35] In addition, sarcopenic patients with diabetes mellitus have been shown to have a large variability in blood presure and a poor prognosis.[36] Nutritional support may be able to prevent cardiovascular events in older patients.[37] As mentioned, underweight is a phenotype, related to various pathophysiological and clinical conditions, and itself is a risk factor for IHCA.

Contrary to our expectation, the IHCA group had low percentages of smoking, hypertension, diabetes mellitus, and dyslipidemia. The IHCA group had lower percentages of renin-angiotensin-aldosterone system agents, β-blockers, antiplatelets, anticoagulants, and statins. For the incidence of cerebro- and cardiovascular disease, both low BMI and high BMI are risk factors. Hypertension, diabetes, and dyslipidemia are also risk factors. These risk factors are considerable for the incidence of IHCA, but in this study patients with low BMI, no underlying disease, and not treated medically showed a high incidence of IHCA. Thus, cerebro- and cardiovascular disease patients with frailty, sarcopenia, and cardiac cachexia and not being treated with cardioprotective drugs might have a greater risk of IHCA.

The IHCA group also had high percentages of CCB and diuretic use. Previous reports have shown that short-acting calcium antagonists are associated with increased risks of cardiovascular events and death.[37–39] In this study, we could not distinguish between short-acting and long-acting CCBs, so this may have affected the incidence of IHCA. It has also been reported that long-term diuretic use is associated with high mortality rates, depending on the clinical situation.[40–42] This may have also influenced the results of this study. In the IHCA group, the percentage of admission by ambulance was high and critical diseases on admission included heart failure, cerebral infarction, acute myocardial infarction, aortic aneurysm and dissection, and intracerebral hemorrhage. These results matched established theory.[2]

Study Limitations

First, some data on BMI were missing, possibly because in emergency cases there was not enough time to measure body weight due to the need for emergency operation or catheter therapy. We excluded 7.27% cases with missing or abnormal BMI data; however, the data for 7,571,826 cases would overcome the missing cases. Second, the JROAD-DPC database did not include data on laboratory examinations, socioeconomic status, or possession of a living will. If we could exclude patients with Do Not Resuscitate orders, the results might change. Analyses by type of hospitals and specialties of each hospital will be needed in future. Socioeconomic status has been reported to be associated with IHCA,[8] but this would have been unlikely to greatly affect the present results, because Japan offers universal health insurance. Third, JROAD-DPC did not include all of the institutes in Japan. The data pool is still substantial because JROAD-DPC obtained data from approximately 1,200 institutes, including ≥70% of DPC hospitals in Japan. Fourth, we did not investigate the association between IHCA and BMI by specific disease. However, another research group has shown similar results for the association of acute cardiovascular diseases with underweight and high in-hospital mortality rates, regardless of the disease, in Japan.[43] Fifth, this was an observational study. Further study is needed to investigate the effect of interventions for low BMI patients against IHCA.

In conclusion, underweight, rather than obese, might be an independent risk factor for IHCA in patients with cerebro- and cardiovascular diseases in an aging society.

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Disclosures

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IRB Information

The study was approved by the Independent Review Board of Fukuoka University (U20-597).

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Supplementary Files

Please find supplementary file(s);
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