

ORIGINAL RESEARCH

# Low Insulin Is an Independent Predictor of All-Cause and Cardiovascular Death in Acute Decompensated Heart Failure Patients Without Diabetes Mellitus

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**BACKGROUND:** Insulin beneficially affects myocardial functions during myocardial ischemia. It increases glucose-derived ATP production, decreases oxygen consumption, suppresses apoptosis of cardiomyocytes, and promotes the survival of cardiomyocytes. Patients with chronic heart failure generally have high insulin resistance, which is correlated with poor outcomes. The role of insulin in acute decompensated heart failure (ADHF) remains unclear. This study aimed to investigate the prognostic value of serum insulin level at the time of admission for long-term outcomes in patients with ADHF.

**METHODS AND RESULTS:** We enrolled 1074 consecutive patients who were admitted to our department for ADHF. Of these 1074 patients, we studied the impact of insulin on the prognosis of ADHF in 241 patients without diabetes mellitus. The patients were divided into groups according to low, intermediate, and high tertiles of serum insulin levels. Primary end points were all-cause death and cardiovascular death. During a mean follow-up of 21.8 months, 71 all-cause deaths and 38 cardiovascular deaths occurred. Kaplan–Meier analysis showed that all-cause and cardiovascular mortality was significantly higher in the low-insulin group than those in the intermediate- and high-insulin groups (log-rank  $P=0.0046$  and  $P=0.038$ , respectively). Moreover, according to the multivariable analysis, low serum insulin was an independent predictor of all-cause and cardiovascular mortality (hazard ratio, 2.37 [95% CI, 1.24–4.65;  $P=0.009$ ] and 2.94 [95% CI, 1.12–8.19;  $P=0.028$ ], respectively).

**CONCLUSIONS:** Low serum insulin levels were associated with increased risk of all-cause and cardiovascular death in ADHF patients without diabetes mellitus.

**Key Words:** acute heart failure ■ diabetes mellitus ■ insulin ■ prognosis

Insulin is generally known as an anabolic hormone, but it is also known as a pleiotropic hormone with various effects on the central nervous, immune, and cardiovascular systems.<sup>1</sup> In addition to promoting glucose uptake in the skeletal muscle and liver, insulin also targets the heart to control energy metabolism.<sup>2</sup> Glucose oxidation demands less oxygen than fatty acid oxidation to produce equivalent amounts of ATP.<sup>3</sup> Therefore, during myocardial ischemia, insulin

promotes glucose as the main cardiac energy substrate, reduces myocardial  $O_2$  consumption, and increases cardiac efficiency. Moreover, it beneficially affects myocardial functions through suppressing apoptosis and promoting survival of cardiomyocytes.<sup>3</sup>

However, many patients with heart failure (HF) have high insulin concentrations and insulin resistance.<sup>4</sup> In patients with chronic HF, insulin resistance is associated with worse prognosis and quality of life.<sup>4,5</sup>

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## CLINICAL PERSPECTIVE

### What Is New?

- This study was the first to demonstrate an association between serum insulin level on admission and long-term outcomes in acute decompensated heart failure patients.
- Low serum insulin level is associated with all-cause mortality and cardiovascular mortality in acute decompensated heart failure patients without diabetes mellitus.

### What Are the Clinical Implications?

- Serum insulin level on admission can predict long-term mortality and be useful in risk stratification among acute decompensated heart failure patients without diabetes mellitus.

## Nonstandard Abbreviations and Acronyms

<b>ADHF</b>	acute decompensated heart failure
<b>BMI</b>	body mass index
<b>BNP</b>	brain natriuretic peptide
<b>GIK</b>	glucose–insulin–potassium
<b>HF</b>	heart failure
<b>HR</b>	hazard ratio
<b>IL</b>	interleukin
<b>NARA-HF</b>	Nara Registry and Analyses for Heart Failure
<b>TNF-<math>\alpha</math></b>	tumor necrosis factor $\alpha$

Several previous studies revealed an increase in plasma insulin levels in acute and severe conditions.<sup>6,7</sup> For example, plasma insulin levels were significantly higher in septic nondiabetic patients than in healthy volunteers.<sup>6</sup> After severe burns, serum insulin levels significantly increased during the acute phase.<sup>7</sup> Patients with critical illness and high or low insulin blood levels had higher in-hospital mortality than patients with normal values.<sup>8</sup>

It remains unclear whether serum insulin levels increase or decrease in patients with acute decompensated HF (ADHF). In addition, the predictive value of serum insulin levels for long-term outcome in those patients with ADHF is still unknown. Therefore, the present study aimed to investigate whether serum insulin levels observed at the time of admission predict long-term mortality in patients with ADHF.

## METHODS

The data, analytic methods, and study materials will not be made available to any researchers for purposes of reproducing the results or replicating the procedure.

### Patients and Ethical Considerations

This study investigated ADHF patients from the NARA-HF 3 (Nara Registry and Analyses for Heart Failure 3) study. The NARA-HF 3 study recruited 1074 consecutive patients following emergency admission to our department for ADHF between January 2007 and December 2016, as described previously.<sup>9–12</sup> The follow-up period ended in July 2017. Diagnosis of HF was based on the criteria of the Framingham study.<sup>13</sup> Patients with acute myocardial infarction, acute myocarditis, and acute HF with acute pulmonary embolism were excluded.

Of the recruited 1074 patients, 622 patients did not have diabetes mellitus and 452 had diabetes mellitus. We excluded patients who did not perform insulin measurements at the time of admission. Serum insulin levels were measured in 241 of 622 patients who did not have diabetes mellitus and in 171 of 452 patients with diabetes mellitus. The detailed flowchart of this study population is presented in Figure 1. We investigated the impact of serum insulin levels on the prognosis of ADHF in 241 patients without diabetes mellitus and 171 patients with diabetes mellitus. The enrolled patients were divided into groups based on low, intermediate, and high tertiles of serum insulin level at the time of admission.

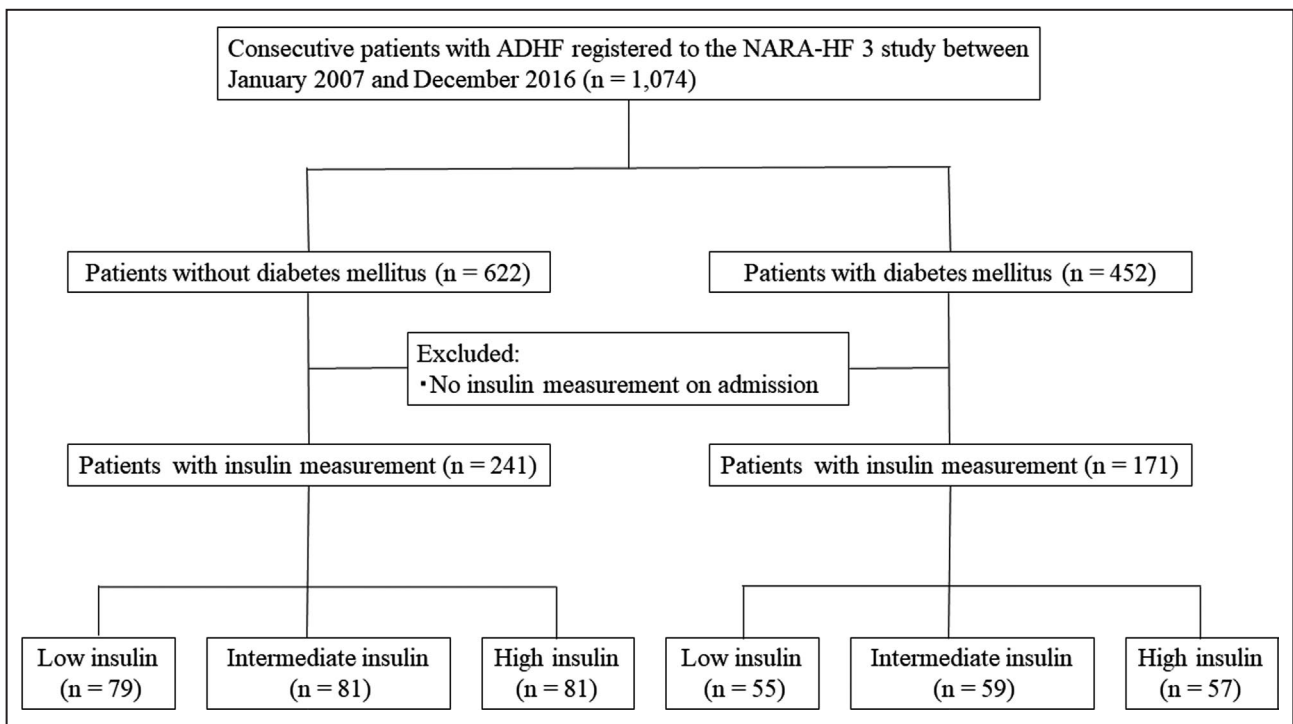
This study was approved by the Nara Medical University Institutional Ethics Committee and was performed in accordance with the 1975 Declaration of Helsinki guidelines for clinical research protocols. Informed consent was obtained from all patients.

### Outcomes

Primary end points were all-cause death and cardiovascular death. Vital status and cause of death were examined through patients' medical records by clinicians blinded to patients' serum insulin levels. When this information was unavailable, blinded clinicians sent letters to the homes of the patients or telephoned the patients or their families.

### Laboratory Findings

Laboratory examinations and echocardiography were performed on all patients at the time of admission. Serum insulin levels were measured using the Cobas Elecsys insulin assay (Roche Diagnostics). The value of glycosylated hemoglobin



**Figure 1. Study population.**

ADHF indicates acute decompensated heart failure; and NARA-HF 3, Nara Registry and Analyses for Heart Failure 3.

A<sub>1c</sub> was converted to a National Standardization Program for Glycosylated Hemoglobin–equivalent value.

**Statistical Analysis**

Normally distributed variables are expressed as mean±SD, whereas nonnormally distributed variables are expressed as median and interquartile range. Categorical variables are expressed using numbers and percentages. Differences between the groups were evaluated using the 1-way ANOVA, Kruskal–Wallis test, or  $\chi^2$  test, as appropriate. Cumulative event-free rates during follow-up were calculated using the Kaplan–Meier method. Differences in event-free survival rates were tested using the log-rank test. Cox proportional hazards models were utilized to examine the associations between serum insulin levels and outcomes after adjusting for covariates, as follows: model 1 was adjusted for age and sex; model 2 was adjusted for all factors in model 1 plus body mass index (BMI), systolic blood pressure, hemoglobin, estimated glomerular filtration rate, sodium levels, and brain natriuretic peptide (BNP) levels. To determine those variables that jointly affected serum insulin levels, multiple linear regression was used to fit a multiple variable model that included variables with  $P < 0.1$  in single-variable linear regression analysis.  $P < 0.05$

was considered statistically significant. JMP software for Windows v12 (SAS Institute) was used for all statistical analyses.

**RESULTS**

**Baseline Characteristics**

Among the 241 patients without diabetes mellitus, the mean age was 75±13 years, and 53% of the patients were male (Table 1). To investigate the impact of insulin on prognosis of ADHF, we divided the patients into tertiles, with dividing points at 4.0 and 7.9  $\mu\text{U}/\text{mL}$ .

The characteristics of patients among tertiles were broadly similar (Table 1). There were no significant differences in age, sex, HF etiology, and use of medication at the time of admission. Compared with the intermediate- and high-insulin groups, the low-insulin group had lower BMI; lower levels of glucose, total protein, and albumin; and higher BNP level. There were differences in serum creatinine levels, estimated glomerular filtration rates, and potassium levels among tertiles.

The mean age of the 171 patients with diabetes mellitus was 75±11 years, and 60% of the patients were male (Table 2). The 171 patients were divided into tertiles, with 4.0 and 10.0  $\mu\text{U}/\text{mL}$  as the dividing points.

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**Table 1. Baseline Characteristics of Patients Without Diabetes Mellitus**

Characteristic	Total (n=241)	Insulin Level, $\mu\text{U/mL}$			P Value
		<4.0 (n=79)	4.0 to <7.9 (n=81)	$\geq 7.9$ (n=81)	
Age, y	75 $\pm$ 13	76 $\pm$ 13	75 $\pm$ 13	74 $\pm$ 12	0.67
Male, n (%)	128 (53)	45 (57)	43 (53)	40 (49)	0.63
BMI, kg/m <sup>2</sup>	22.7 $\pm$ 4.0	21.3 $\pm$ 3.3	22.9 $\pm$ 4.1	23.7 $\pm$ 4.1	0.0006
Heart rate, beats/min	104 $\pm$ 31	102 $\pm$ 27	105 $\pm$ 33	104 $\pm$ 32	0.81
Systolic blood pressure, mm Hg	148 $\pm$ 37	147 $\pm$ 36	149 $\pm$ 35	147 $\pm$ 40	0.85
Diastolic blood pressure, mm Hg	89 $\pm$ 26	88 $\pm$ 21	88 $\pm$ 21	89 $\pm$ 33	0.97
NYHA class III or IV, n (%)	225 (94)	73 (94)	75 (93)	77 (96)	0.59
Heart failure etiology, n (%)					
Ischemic	63 (26)	22 (28)	26 (32)	15 (19)	0.14
Dilated cardiomyopathy	39 (16)	12 (15)	13 (16)	14 (18)	0.93
Valve disease	57 (24)	20 (26)	13 (16)	24 (30)	0.1
Hypertension	12 (5)	3 (4)	4 (5)	5 (6)	0.79
Comorbid conditions, n (%)					
Previous HF hospitalization	55 (23)	19 (24)	22 (27)	14 (17)	0.31
Hypertension	161 (67)	47 (59)	54 (67)	60 (75)	0.11
Dyslipidemia	71 (30)	22 (28)	25 (32)	24 (31)	0.88
Previous myocardial infarction	44 (18)	14 (18)	18 (22)	12 (15)	0.47
Atrial fibrillation	110 (46)	31 (40)	35 (43)	44 (55)	0.13
Laboratory data					
Hemoglobin, g/dL	11.9 $\pm$ 2.3	11.8 $\pm$ 2.2	11.9 $\pm$ 2.4	12.0 $\pm$ 2.4	0.78
Creatinine, mg/dL	1.1 (0.8–1.5)	1 (0.8–1.6)	0.9 (0.7–1.4)	1.2 (0.9–1.7)	0.0093
eGFR, mL/min/1.73 m <sup>2</sup>	49.2 $\pm$ 25.2	50.3 $\pm$ 28.6	55.5 $\pm$ 25.1	41.9 $\pm$ 19.4	0.0022
Glucose, mg/dL	118 $\pm$ 47	96 $\pm$ 21	112 $\pm$ 31	146 $\pm$ 61	<0.0001
Insulin, $\mu\text{U/mL}$	5.7 (3.3–10.4)	2.7 (1.9–3.2)	5.7 (4.8–6.7)	13.5 (10.4–24.7)	<0.0001
Hemoglobin A <sub>1c</sub> , %	5.7 $\pm$ 0.4	5.6 $\pm$ 0.4	5.7 $\pm$ 0.4	5.7 $\pm$ 0.5	0.074
Sodium, mmol/L	138 $\pm$ 4	139 $\pm$ 3	138 $\pm$ 5	138 $\pm$ 5	0.36
Potassium, mmol/L	4.2 $\pm$ 0.6	4.2 $\pm$ 0.1	4.0 $\pm$ 0.1	4.3 $\pm$ 0.1	0.02
BNP, pg/mL	1025 (452–1821)	1301 (641–2000)	988 (522–1930)	796 (339–1266)	0.0004
TP, g/dL	6.7 $\pm$ 0.7	6.5 $\pm$ 0.1	6.8 $\pm$ 0.1	6.8 $\pm$ 0.1	0.002
Albumin, g/dL	3.8 $\pm$ 0.5	3.5 $\pm$ 0.1	3.8 $\pm$ 0.1	3.9 $\pm$ 0.1	<0.0001
LVEF, %	43 $\pm$ 17	41 $\pm$ 15	42 $\pm$ 17	45 $\pm$ 18	0.19
Medication, n (%)					
$\beta$ -blocker	82 (34)	25 (32)	25 (31)	32 (40)	0.44
ACE-I or ARB	116 (48)	33 (42)	38 (47)	45 (56)	0.21
Diuretic	112 (47)	36 (46)	32 (40)	44 (54)	0.17
Spironolactone	40 (17)	13 (17)	11 (14)	16 (21)	0.5

Data are shown as number (%), mean $\pm$ SD, or median (interquartile range). P value is from ANOVA across the 3 insulin level groups. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and TP, total protein.

The characteristics of the 171 patients are shown in Table 2. Compared with the intermediate- and high-insulin groups, the low-insulin group was older and had lower proportions of patients who had dyslipidemia and who were with angiotensin-converting enzyme inhibitors

and/or angiotensin II receptor blockers. The low-insulin group similarly had lower BMI and lower levels of glucose, total protein, and albumin than those without diabetes mellitus. There were differences in the proportion of valve disease and previous myocardial infarction.

**Table 2. Baseline Characteristics of Patients With Diabetes Mellitus**

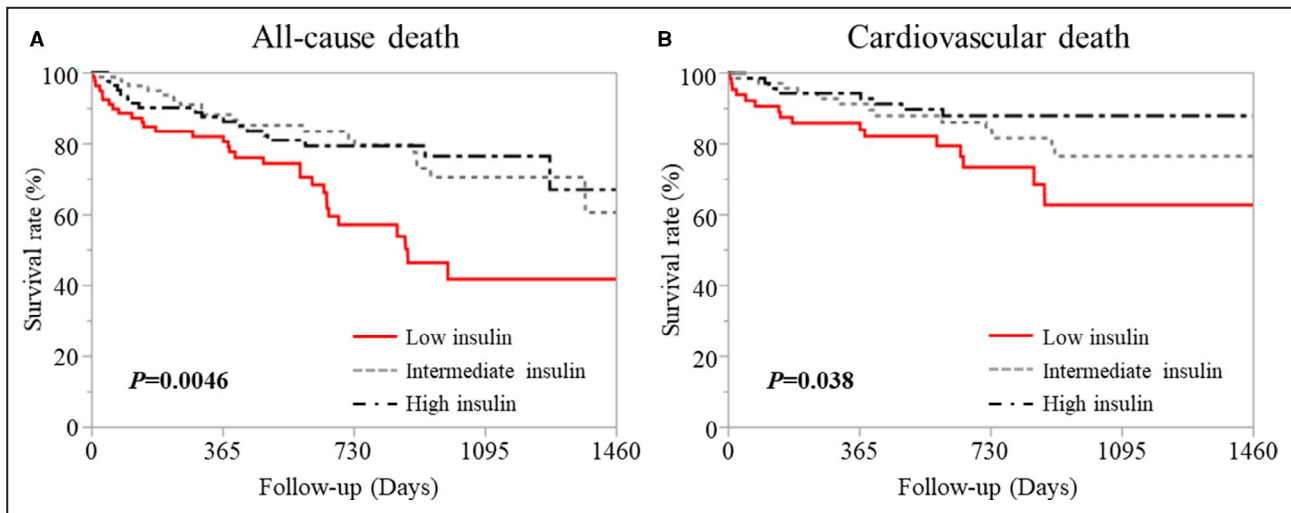
Characteristic	Total (n=171)	Insulin Level, $\mu\text{U/mL}$			P Value
		<4.0 (n=55)	4.0 to <10 (n=59)	$\geq 10$ (n=57)	
Age, y	75 $\pm$ 11	77 $\pm$ 10	73 $\pm$ 12	71 $\pm$ 11	0.036
Male, n (%)	103 (60)	37 (67)	35 (59)	31 (54)	0.37
BMI, kg/m <sup>2</sup>	23.9 $\pm$ 4.4	22.9 $\pm$ 4.8	24.6 $\pm$ 3.9	25.0 $\pm$ 4.4	0.032
Heart rate, beats/min	96 $\pm$ 27	94 $\pm$ 27	103 $\pm$ 28	98 $\pm$ 25	0.22
Systolic blood pressure, mm Hg	150 $\pm$ 36	154 $\pm$ 37	149 $\pm$ 34	150 $\pm$ 38	0.8
Diastolic blood pressure, mm Hg	82 $\pm$ 24	86 $\pm$ 23	83 $\pm$ 23	87 $\pm$ 26	0.63
NYHA class III or IV, n (%)	140 (91)	47 (92)	48 (91)	45 (90)	0.93
Heart failure etiology, n (%)					
Ischemic	68 (44)	22 (44)	19 (35)	27 (54)	0.16
Dilated cardiomyopathy	22 (14)	8 (16)	9 (17)	5 (10)	0.57
Valve disease	21 (14)	2 (4)	13 (24)	6 (12)	0.011
Hypertension	12 (8)	4 (8)	3 (6)	5 (10)	0.7
Comorbid conditions, n (%)					
Previous HF hospitalization	36 (21)	9 (17)	12 (21)	15 (26)	0.46
Hypertension	129 (77)	43 (78)	43 (75)	43 (78)	0.92
Dyslipidemia	89 (55)	24 (45)	26 (46)	39 (72)	0.006
Previous myocardial infarction	49 (29)	13 (24)	9 (15)	27 (48)	0.0003
Atrial fibrillation	59 (38)	24 (47)	22 (40)	13 (27)	0.1
Laboratory data					
Hemoglobin, g/dL	11.4 $\pm$ 2.4	11.6 $\pm$ 2.6	11.2 $\pm$ 2.4	11.9 $\pm$ 2.3	0.31
Creatinine, mg/dL	1.3 (0.9–2.2)	1.4 (0.9–2.0)	1.1 (0.9–1.8)	1.3 (0.9–2.9)	0.17
eGFR, mL/min/1.73 m <sup>2</sup>	39.0 $\pm$ 23.9	42.2 $\pm$ 24.5	44.8 $\pm$ 23.8	35.9 $\pm$ 23.1	0.12
Glucose, mg/dL	139 $\pm$ 74	128 $\pm$ 63	164 $\pm$ 80	194 $\pm$ 63	<0.0001
Insulin, $\mu\text{U/mL}$	6.4 (3.1–13.6)	2.1 (1.6–3.1)	6.3 (4.9–8.1)	19.7 (13.3–31.6)	<0.0001
Hemoglobin A <sub>1c</sub> , %	6.7 $\pm$ 1.4	6.8 $\pm$ 1.6	7.0 $\pm$ 1.6	6.8 $\pm$ 0.9	0.72
Sodium, mmol/L	138 $\pm$ 5	137 $\pm$ 5	137 $\pm$ 5	138 $\pm$ 4	0.27
Potassium, mmol/L	4.3 $\pm$ 0.7	4.4 $\pm$ 0.7	4.3 $\pm$ 0.8	4.4 $\pm$ 0.7	0.99
BNP, pg/mL	924 (579–1692)	1265 (721–2000)	791 (488–1667)	895 (582–1403)	0.12
TP, g/dL	6.6 $\pm$ 0.7	6.3 $\pm$ 0.7	6.7 $\pm$ 0.7	6.7 $\pm$ 0.7	0.0026
Albumin, g/dL	3.6 $\pm$ 0.5	3.4 $\pm$ 0.5	3.7 $\pm$ 0.5	3.8 $\pm$ 0.5	0.001
LVEF, %	41 $\pm$ 16	43 $\pm$ 17	47 $\pm$ 16	41 $\pm$ 16	0.17
Medication, n (%)					
$\beta$ -blocker	59 (38)	15 (29)	23 (42)	21 (42)	0.28
ACE-I or ARB	82 (52)	21 (40)	24 (44)	37 (74)	0.0009
Diuretic	74 (47)	25 (49)	25 (45)	24 (48)	0.93
Spironolactone	27 (18)	9 (18)	11 (20)	7 (14)	0.74

P value is from an ANOVA across the 3 insulin level groups. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and TP, total protein.

## Prognosis and Outcomes

During a mean follow-up period of 21.8 months, there were 71 all-cause deaths and 38 cardiovascular deaths in patients without diabetes mellitus. There were 58 all-cause deaths and 28 cardiovascular deaths among patients with diabetes mellitus during a mean follow-up period of 17.1 months. Kaplan-Meier

curves are shown in Figure 2. Among those without diabetes mellitus, the rates of all-cause and cardiovascular mortality were significantly higher in the low-insulin group than those in the intermediate- and high-insulin groups (log-rank  $P=0.0046$  and  $P=0.038$ , respectively) (Figure 2A and 2B). In contrast, there were no significant differences in mortality among the



**Figure 2.** Kaplan–Meier curves for (A) all-cause and (B) cardiovascular death according to serum insulin levels at the time of admission among patients without diabetes mellitus. Low,  $<4 \mu\text{U/mL}$ ; intermediate,  $4\text{--}7.9 \mu\text{U/mL}$ ; high,  $\geq 7.9 \mu\text{U/mL}$ .

tertiles in patients with diabetes mellitus (Figure 3A and 3B).

Table 2 shows the unadjusted and adjusted hazard ratios (HR) for all-cause and cardiovascular mortality in patients without diabetes mellitus. According to the univariate analysis, low insulin was associated with a higher rate of all-cause and cardiovascular death in comparison to high insulin (HR, 2.34 [95% CI, 1.32–4.27;  $P=0.0036$ ] and 2.9 [95% CI, 1.27–7.17;  $P=0.011$ ], respectively). According to the multivariate Cox proportional hazard regression models, low insulin was also a predictor of increased all-cause and cardiovascular mortality after adjustment for covariates (Table 3). In contrast, there was no association between intermediate insulin levels and outcomes.

### Factors Affecting Insulin

We also performed multiple linear regression to identify factors affecting insulin (Table 4). Insulin level was associated with age, BMI, hemoglobin, BNP, glucose, adrenocorticotrophic hormone, cortisol, renin, aldosterone, and albumin, according to the single linear regression analysis. The full multiple linear regression was performed for the variables with  $P<0.1$  on single linear regression analysis. Based on the full multiple linear regression analysis, BMI, BNP, glucose, renin, and albumin were independent predictors of insulin level. Insulin level was positively correlated with BMI, glucose, renin, and albumin, whereas it was negatively correlated with BNP level. We further conducted the minimal multiple linear regression, using stepwise backward regression modeling. The minimal multiple model demonstrated that sex, BMI, BNP, glucose, and renin were associated with insulin level.

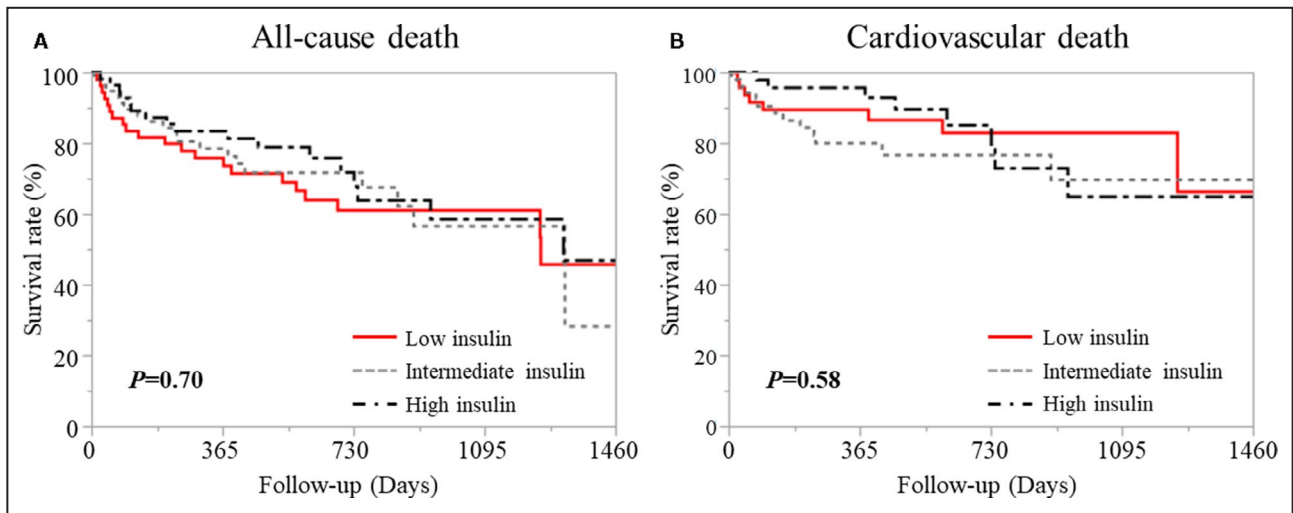
### DISCUSSION

This study showed that among patients without diabetes mellitus, all-cause and cardiovascular mortality were significantly higher in the low-insulin group than those in the intermediate- and high-insulin groups. Furthermore, the multivariable analysis showed that low serum insulin was an independent predictor of all-cause and cardiovascular mortality.

In the diabetic group, there were no differences in mortality among the tertiles. Also in the diabetic group, most patients had already received insulin or glucose-lowering agents on admission, so serum insulin level at the time of admission was presumed to be affected by insulin or glucose-lowering agents.

A previous study revealed that insulin level is associated with in-hospital mortality in patients admitted for serious illnesses, such as sepsis, trauma, respiratory failure, and cardiogenic shock.<sup>8</sup> To the best of our knowledge, no studies report associations between insulin levels and mortality for patients with ADHF. The present study was the first to establish an association between serum insulin levels at the time of admission and all-cause mortality and cardiovascular mortality in ADHF patients without diabetes mellitus. However, it remains unclear why low insulin levels at the time of admission are associated with poor outcomes.

In the present study, pulse rate, systolic blood pressure, and New York Heart Association classification were similar among the tertiles; therefore, we concluded that there were no differences in the severity of HF and stress. Blood glucose and insulin levels were temporarily elevated in the acute phase of serious diseases, and it is known that insulin plays a key role in myocardial adaptation to stress.<sup>14</sup> No transient elevation of insulin levels in the acute phase



**Figure 3.** Kaplan–Meier curves for (A) all-cause and (B) cardiovascular death according to serum insulin levels at the time of admission among patients with diabetes mellitus. Low, <4 μU/mL; intermediate, 4–7.9 μU/mL; high, ≥7.9 μU/mL.

was related to an impaired reaction to stress. In the low-insulin group, the metabolic reaction to stress was impaired, and it was hypothesized that the impairment would be associated with poor outcomes. There were more sudden cardiac deaths in the low-insulin group than in the intermediate- and high-insulin groups; this was also related to an impaired reaction to stress.

In the present study, the low-insulin group had lower BMI and lower serum albumin level compared with the other groups. Protein malnutrition reduces insulin synthesis, release, and peripheral sensitivity in β cells.<sup>15</sup> Malnutrition is associated with adverse outcomes in HF.<sup>16,17</sup> Thus, these findings indicate that the low-insulin group in our study might be in a low-nutrient state.

The low-insulin group had also lower BMI and higher BNP than the other groups in this study. Sugisawa et al<sup>18</sup> reported that BNP was inversely associated with BMI. The relationship between low insulin and

high BNP seems to be modified by BMI. However, in the multivariate linear regression analysis, insulin level was independently correlated with BMI and BNP level. The relationship between insulin and BNP is not fully explained, and more research is required to confirm these relationships.

Jeschke MG et al<sup>7</sup> reported that burn injury increases inflammatory response, whereas insulin decreased serum IL-6 (interleukin 6), cytokine-induced neutrophil chemoattractants 1 and 2, and macrophage inflammatory protein following burn. Insulin given during the acute phase improved not only acute hospital outcomes but also long-term outcome during a period of 1 year.<sup>7</sup> Many inflammatory cytokines such as TNF-α (tumor necrosis factor α), IL-6, and IL-18 are elevated during HF.<sup>19–21</sup> IL-6 levels in ADHF patients were significantly higher than in controls.<sup>22</sup> In ADHF, insulin also decreases the inflammatory response, which might relate to good prognosis in the high-insulin group in the present study.

**Table 3.** Univariate and Multivariate Cox Regression Analysis for Outcomes in Patients Stratified by Serum Insulin Levels

	Low Insulin (Insulin <4.0 μU/mL)		Intermediate Insulin (4.0 to <7.9 μU/mL)		High Insulin (≥7.9 μU/mL)
	HR (95% CI)	P Value	HR (95% CI)	P Value	
All cause death					
Unadjusted	2.34 (1.32–4.27)	0.0036	1.15 (0.61–2.19)	0.66	1
Adjusted	2.37 (1.24–4.65)	0.009	1.15 (0.59–2.29)	0.68	1
Cardiovascular death					
Unadjusted	2.90 (1.27–7.17)	0.011	1.77 (0.76–4.44)	0.19	1
Adjusted	2.94 (1.12–8.19)	0.028	1.35 (0.53–3.61)	0.53	1

Cox proportional hazards model adjusted for age, sex, body mass index, systolic blood pressure, hemoglobin, estimated glomerular filtration rate, sodium, and brain natriuretic peptide. HR indicates hazard ratio.

**Table 4. Single- and Multiple-Variable Linear Regression Analyses of Serum Insulin Levels**

	Single Variable			Full Multiple Variable			Minimal Multiple Variable		
	$\beta$	95% CI	P Value	$\beta$	95% CI	P Value	$\beta$	95% CI	P Value
Age	-0.16	-0.29 to -0.025	0.02	0.057	-0.067 to 0.18	0.37			
Sex, female (vs male)	-0.48	-1.23 to 2.20	0.58				1.58	0.32 to 2.85	0.014
BMI, kg/m <sup>2</sup>	0.58	0.15-1.00	0.0084	0.44	0.082-0.80	0.016	0.46	0.14-0.79	0.0057
Hemoglobin, g/dL	0.90	0.17-1.63	0.016	0.14	-0.50 to 0.78	0.6			
eGFR, mL/min/1.73 m <sup>2</sup>	-0.02	-0.085 to 0.052	0.63						
Sodium, mmol/L	-0.10	-0.51 to 0.30	0.61						
BNP, pg/mL	-0.002	-0.0037 to -0.0004	0.018	-0.0014	-0.0027 to -0.0001	0.030	-0.0016	-0.0029 to -0.0004	0.0095
LVEF, %	0.023	-0.070 to 0.13	0.66						
Glucose, mg/dL	0.098	0.063-0.13	<0.0001	0.058	0.028-0.088	0.0002	0.075	0.049-0.10	<0.0001
Hemoglobin A <sub>1c</sub> , %	2.15	-1.26 to 5.57	0.22						
ACTH, pg/mL	0.02	0.0068-0.037	0.0047	0.0071	-0.0080 to 0.022	0.36			
Cortisol, $\mu$ g/dL	0.082	0.022-0.14	0.0078	0.051	-0.0033 to 0.11	0.065			
Renin, ng/mL per h	0.18	0.079-0.28	0.0005	0.16	0.056-0.26	0.00	0.18	0.085-0.27	0.0002
Aldosterone, pg/mL	0.0073	0.0010-0.014	0.023	0.0023	-0.0042 to 0.0088	0.490			
CRP, mg/dL	0.15	-0.53 to 0.84	0.66						
Albumin, g/dL	5.49	1.97-8.98	0.0022	3.39	0.40-6.38	0.026			

ACTH indicates adrenocorticotropic hormone; BMI, body mass index; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; and LVEF, left ventricular ejection fraction.



Sodi-Pallares et al<sup>23</sup> reported the use of glucose–insulin–potassium (GIK) infusion for the treatment of acute myocardial infarction. Since then, the effects of GIK on the heart have been studied, with mixed reports regarding clinical benefits of GIK.<sup>24–27</sup> Insulin inhibits the activity of peripheral lipase and decreases intracellular cAMP concentrations in adipose tissue, and this interferes with  $\beta$ -adrenergic signaling and attenuates catecholamine-stimulated lipolysis.<sup>28</sup> GIK infusion has been shown to lower plasma fatty acid levels; reducing levels of free fatty acids leads to availability for preventing cardiac ischemic injury and arrhythmia.<sup>28</sup> In the present study, high insulin levels might contribute to reduced levels of free fatty acids and be associated with good prognosis. Taking these reports into account, the low insulin level together with the low glucose level might not have led to downregulation of free fatty acids. Further research is necessary to confirm whether GIK infusion have beneficial effects on ADHF patients.

Several reports have confirmed that insulin exerts a cardioprotective effect against myocardial ischemia/reperfusion injury through antiapoptotic and prosurvival signals mediated by PI3K/Akt/mTOR pathways.<sup>29–31</sup> Yang et al<sup>32</sup> reported that microRNA miR-320 is an upstream regulator of survivin and contributes to insulin protection against ischemic-induced myocardial injury. Little has been reported about insulin's effect on ADHF. Insulin could also have cardioprotective effects on ADHF, but further investigation is required to confirm it.

Insulin resistance without diabetes mellitus is also significantly linked to the development of HF.<sup>33</sup> Insulin resistance increases the risk of HF, even after adjusting for traditional risk factors.<sup>34</sup> In general, high insulin levels are correlated with the development of HF. Conversely, in the present study, low insulin levels were associated with poor outcomes. The associations between insulin and HF might differ between acute and chronic HF; however, more research is required to confirm these associations.

## LIMITATIONS

This study has several limitations that should be addressed. First, this was a single-center study with a small sample size; therefore, future prospective studies with larger populations are required. Second, regarding insulin level at the time of admission, we measured serum insulin levels at admission or in the early morning on the day after hospitalization. Regarding patients who had measured serum insulin levels at admission, we did not know the times of their last meal. Not all patients were in a fasting state, and insulin levels were not necessarily influenced by meals. Third, oral glucose tolerance tests were not performed on all patients;

therefore, we may not have excluded all patients with diabetes mellitus and impaired glucose tolerance. Fourth, we did not measure serum insulin levels at the chronic phase, so we were not able to compare the insulin levels in the acute phase with levels in chronic phase to examine insulin sensitivity. In this study, low insulin levels may reflect a physiologic reaction of low glucose concentrations. Further research is necessary to confirm our findings and to elucidate why low insulin levels at the time of admission led to poor patient prognosis.

## CONCLUSIONS

In this study, a low insulin level was associated with an increased risk of all-cause and cardiovascular death in ADHF patients without diabetes mellitus.

## ARTICLE INFORMATION

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