


Original Article

High fever or hypotension predicts non-hypoglycemia in patients with impaired consciousness in prehospital settings

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Aim: To evaluate whether vital signs can predict whether hypoglycemia can be eliminated as the cause of impaired consciousness in prehospital settings.

Methods: We extracted the data of patients who underwent blood glucose measurements by paramedics in Kobe City, Japan from April 2015 to March 2019. We used receiver operating characteristic curves and calculated the area under the curve (AUC) to evaluate the validity of the vital signs in distinguishing hypoglycemia. We also calculated stratum-specific likelihood ratios to examine the threshold at which hypoglycemia becomes less likely for each vital sign.

Results: Of the 1,791 patients, 1,242 were eligible for analysis. Hypoglycemia was observed in 324 patients (26.1%). Significant differences in each vital sign were noted between the hypoglycemic and non-hypoglycemic groups. Body temperature was moderately accurate in differentiating between the two groups (AUC, 0.71; 95% confidence interval, 0.68–0.74). Furthermore, in patients with systolic blood pressure <100 mmHg and body temperature $\geq 38^{\circ}\text{C}$, it was unlikely that hypoglycemia caused impaired consciousness (stratum-specific likelihood ratios 0.12 and 0.15; 95% confidence intervals, 0.05–0.25 and 0.06–0.35, respectively).

Conclusion: In the prehospital assessment of patients with impaired consciousness, high fever or hypotension was helpful in differentiating between hypoglycemia and non-hypoglycemia. In particular, body temperature $\geq 38^{\circ}\text{C}$ or systolic blood pressure <100 mmHg indicated a low likelihood of hypoglycemia. A validation study is needed to confirm the findings in this study.

Key words: Blood glucose level, hypoglycemia, impaired consciousness, prehospital emergency care, vital signs

INTRODUCTION

HYPOGLYCEMIA IS A condition that must be considered in patients with impaired consciousness. In April 2014, Japanese paramedics were officially permitted to measure blood glucose levels in patients with impaired consciousness.¹ Conversely, hypoglycemia is not a common condition in prehospital settings. Only 1–5% of patients requiring emergency transport have severe hypoglycemia that needs immediate treatment,^{2,3} and only 5% of comatose patients have a metabolic etiology such as hypoglycemia.⁴ Thus, paramedics often evaluate blood glucose in patients

with impaired consciousness, even when the patients are unstable on physiological assessment (e.g., in shock), because there are no specific criteria to measure blood glucose other than the level of consciousness. In patients with impaired consciousness, paramedics need to consider many other critical medical conditions such as neurological causes (seizure or stroke), toxicological causes, and infection.^{5,6} In other countries, paramedics are recommended to measure blood glucose for all patients with impaired consciousness.⁶ However, this could be harmful because of resultant delay in transporting the patient to the hospital and in initiating treatment.

Although a medical history of diabetes mellitus and neurological examination findings can be useful to determine whether hypoglycemia is a potential cause of impaired consciousness,^{2,7,8} it is often difficult to obtain a detailed medical history and undertake a physical examination in the field, especially in such patients. Therefore, it would be beneficial if simple, routine vital signs measurement could distinguish patients with impaired consciousness who are less likely to

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have hypoglycemia. This could save time for patients who require urgent transfer to the hospital more than blood glucose evaluation. Although a few studies have evaluated the changes in vital signs in hypoglycemic patients,^{9–11} there are no reports correlating the vital signs and blood glucose in prehospital settings. In this study, we examined whether vital signs are effective indicators to determine the presence or absence of hypoglycemia as a cause of impaired consciousness in prehospital settings.

METHODS

Study design and cohort

WE UNDERTOOK A retrospective study based on data extracted from the Kobe City Fire Department (Kobe City, Japan) database. Our study group included patients with impaired consciousness for whom paramedics evaluated blood glucose from April 2015 to March 2019. The population of Kobe City is approximately 1.5 million people and the number of patients requiring emergency medical services annually is approximately 73,000.¹² Our hospital is positioned as a main center for emergency medicine, and approximately 10,000 patients annually are transported to it; almost 14% of the total number of emergency medical services patients in Kobe. This study was approved by the ethics board of the Kobe City Medical Centre General Hospital.

Paramedics evaluated blood glucose levels according to the protocol shown in Table 1. We collected the following data: age, sex, Japan Coma Scale (JCS) score, presence of hypoglycemia (defined by Kobe City Fire Department as <50 mg/dL), vital signs (systolic blood pressure [sBP], heart rate [HR], respiratory rate [RR], oxygen saturation by pulse oximetry [SpO₂], and body temperature [BT]). The vital signs collected were the first values recorded by the paramedics. We also collected and verified the final diagnosis for non-hypoglycemic patients transferred to our hospital. We excluded patients under 15 years of age, with errors in blood glucose measurement, or missing data for any vital sign or JCS. We also excluded patients who underwent blood glucose evaluation despite consciousness levels not meeting those of the blood glucose measurement protocol (for example, JCS 0, I-digit code). In Japan, the JCS is used as a scale to evaluate patient consciousness (level 9) and is also used in blood glucose measurement protocols for paramedics.^{13–14} The JCS comprises four categories: 0, I-, II- and III-digit codes. Each code has three subcategories: 1, 2, and 3 in the I-digit code; 10, 20, and 30 in the II-digit code; and 100, 200, and 300 in the III-digit code (Table 1). The I-, II- and III-digit

Table 1. Kobe City Fire Department blood glucose measurement criteria and Japan Coma Scale

Blood glucose measurement protocol	
Patients who satisfy both of the following two conditions:	
1. Recognized impaired consciousness (as a guide \geq Japan Coma Scale II-10)	
2. There is an advantage in identifying consciousness disorder and selecting a hospital by performing blood glucose measurement	
However, if subarachnoid hemorrhage is strongly suspected (and pain stimulation due to skin puncture for blood glucose measurement is considered inappropriate for the patient), it is excluded.	
Level	Grade
Alert	0
The patient is awake without any stimuli, and:	I-digit code
Almost fully conscious	1
Unable to recognize time, place, and person	2
Unable to recall name or date of birth	3
The patient can be aroused, then	II-digit code
reverts to previous state after cessation of stimuli	
Easily with a normal call	10
With loud voice or shaking of shoulders	20
Only with repeated painful stimuli and calls	30
The patient cannot be aroused with any	III-digit code
painful stimuli, and:	
Responds with movements to avoid the stimuli	100
Responds with slight movements including	200
decerebrate and decorticate posture	
Fails to respond	300

codes correspond to E4, E3 or E2, and E1 on the Glasgow Coma Scale, respectively.

Statistical analysis

We compared the differences in vital signs between the hypoglycemic and non-hypoglycemic groups. The χ^2 -test and Mann–Whitney *U*-test were used, and a *P*-value <0.05 was considered significant. The effectiveness of each vital sign in predicting hypoglycemia was analyzed using receiver operating characteristic (ROC) curves, and the area under the curve (AUC) was calculated to estimate diagnostic accuracy. For ease of application in clinical practice and to indicate a threshold for each vital sign, we stratified the continuous values of each vital sign (sBP, HR, RR, SpO₂, and

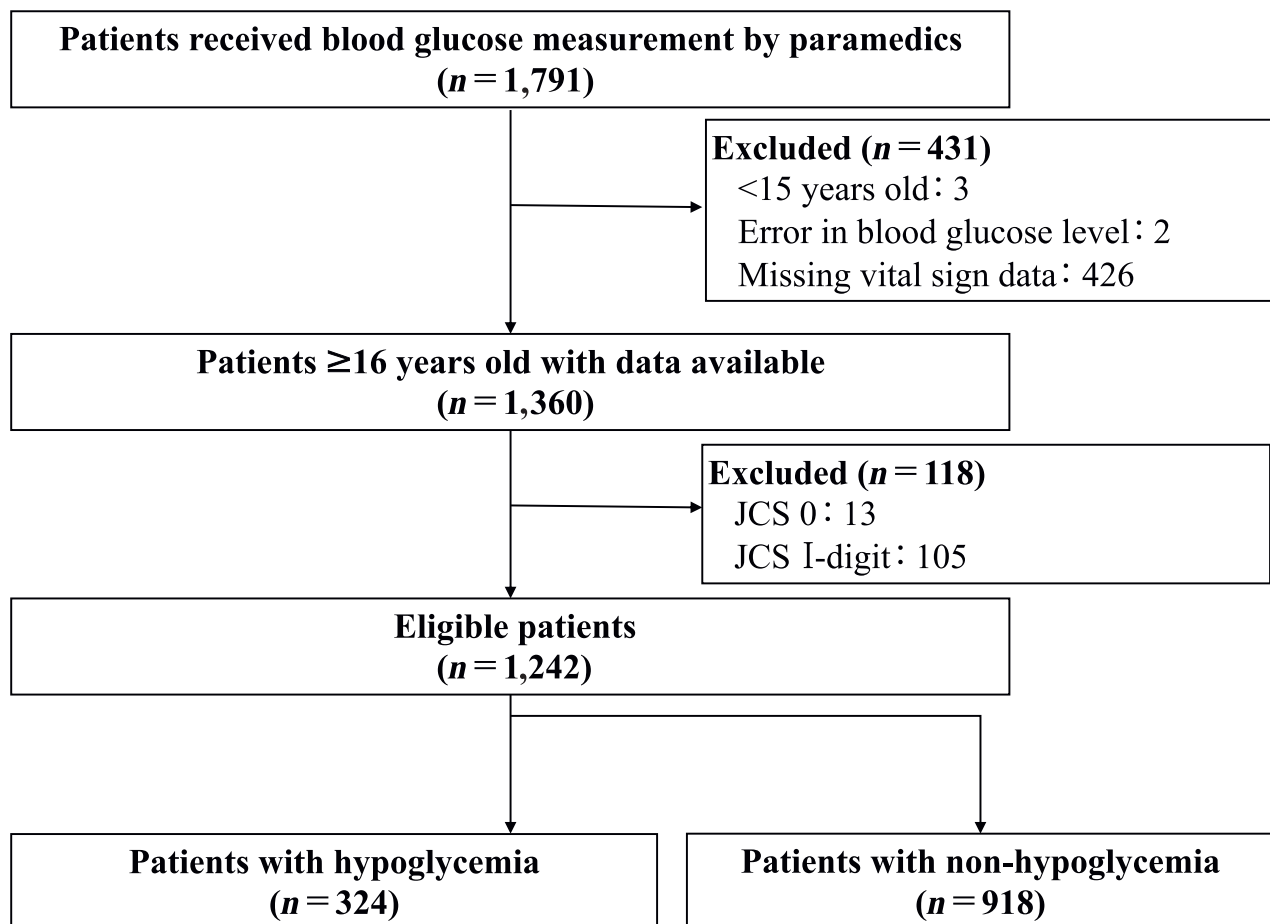


Fig. 1. Flow chart of the study design. JCS, Japan Coma Scale.

Table 2. Characteristics of patients with impaired consciousness in prehospital settings

	Hypoglycemia	Non-hypoglycemia	P-value
N	324	918	
Male sex	191 (59.0)	529 (57.6)	0.69
Age (years)	73 (62–82)	76 (65–84)	<0.01*
sBP (mmHg)	150 (129–170)	136 (110–164)	<0.01*
HR (/min)	80 (70–91.3)	82 (70–100)	0.03*
RR (/min)	20 (18–20)	20 (18–24)	0.03*
SpO2 (%)	96 (95–98)	96 (93–98)	<0.01*
BT (°C)	36.0 (35.5–36.4)	36.5 (36.0–37.0)	<0.01*
JCS			
II-digit code	198 (61.1)	597 (65.0)	0.21
III-digit code	126 (38.9)	321 (35.0)	0.21

Data are shown as *n* (%) or median (interquartile range).

BT, body temperature; HR, heart rate; JCS, Japan Coma Scale; RR, respiratory rate; sBP, systolic blood pressure; SpO2, oxygen saturation by pulse oximetry.

**P* < 0.05 is statistically significant.

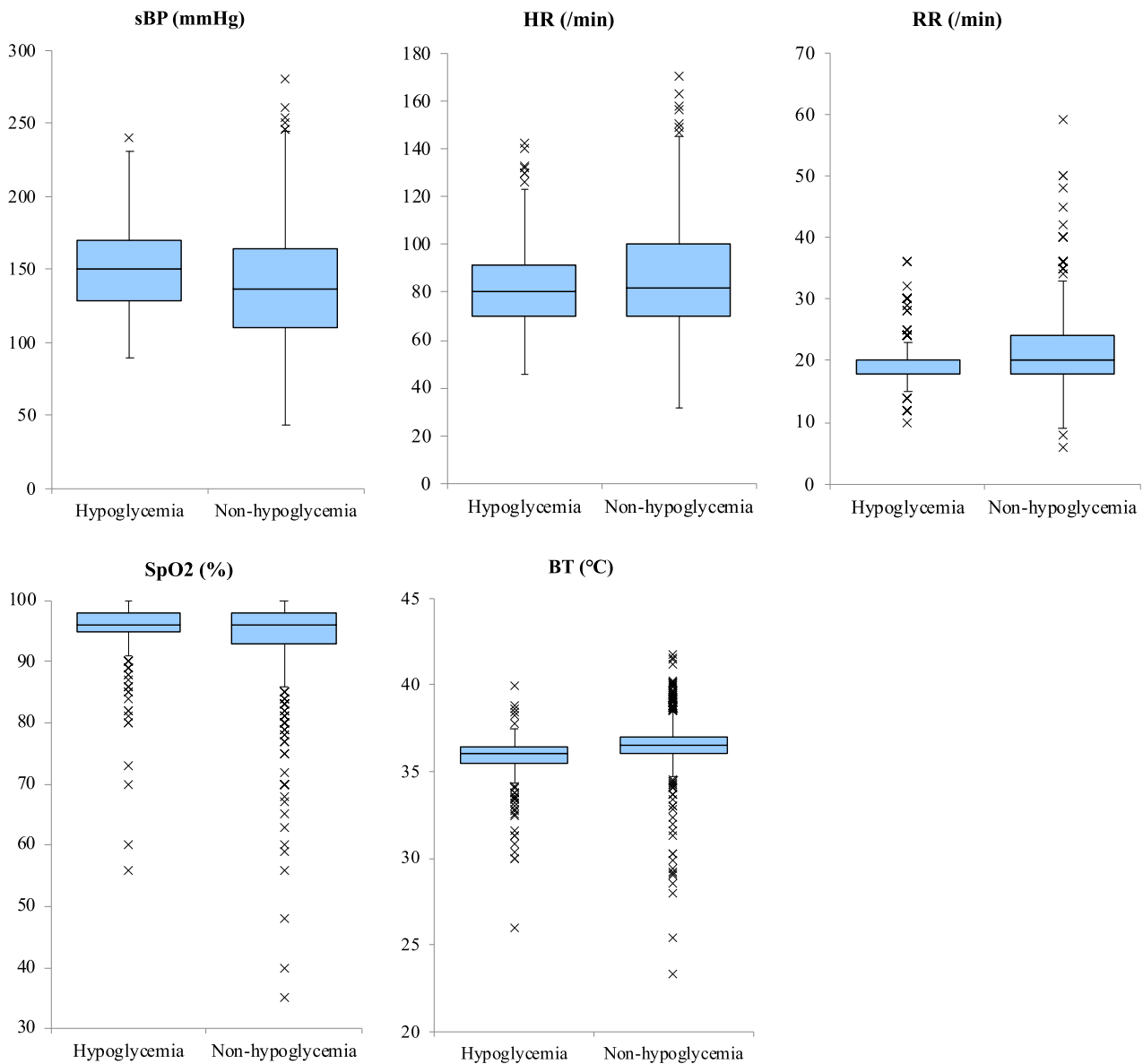


Fig. 2. Distribution of vital signs in patients with impaired consciousness in prehospital settings, grouped according to the presence of hypoglycemia. The bottom to top edge of each box shows the first quartile to third quartile, respectively. The upper and lower whiskers indicate the upper and lower limits of 1.5 times the quartile range, with symbol × indicating outliers. The center line indicates the median. BT, body temperature; HR, heart rate; RR, respiratory rate; sBP, systolic blood pressure; SpO₂, oxygen saturation by pulse oximetry.

BT) into several categories. The stratum-specific likelihood ratio (SSLR) could be used to obtain such categories.¹⁵ The SSLR was then calculated to examine the cut-off value for each vital sign. The SSLR is the probability of a test result in the presence of disease divided by the probability of a test result in the absence of disease.¹⁶ We calculated by the formula $SSLR = (nx / NX) / (ny / NY)$, where nx is the

number of patients in the stratum with hypoglycemia, NX is the total number of patients with hypoglycemia, ny is the number of patients in the stratum with non-hypoglycemia, and NY is the total number of patients with non-hypoglycemia. If the LR is higher than 5 and lower than 0.2, the post-test probability increases or decreases by approximately 30%, respectively, suggesting moderate usefulness for

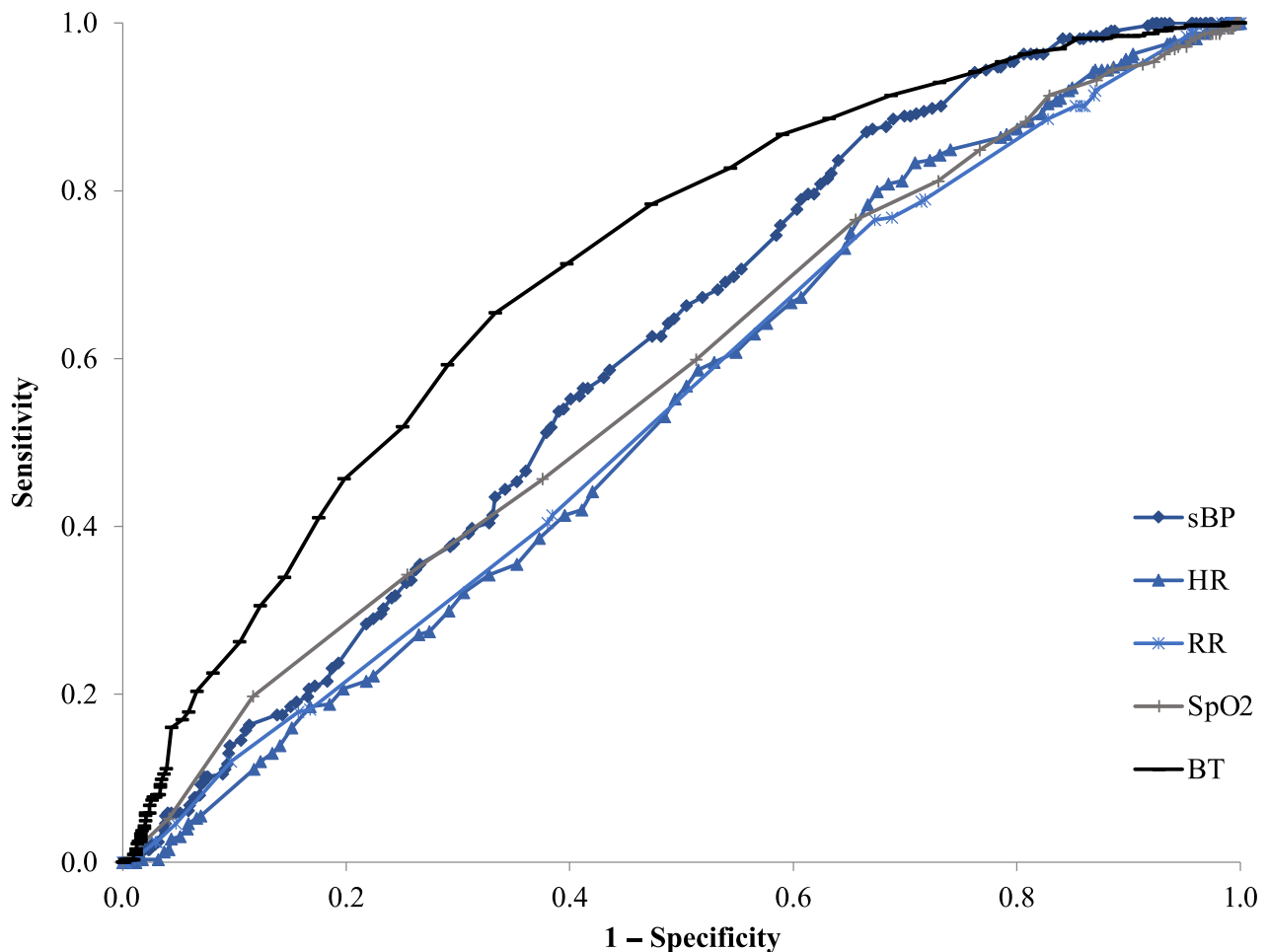


Fig. 3. Receiver operating characteristic curve for each vital sign among patients with impaired consciousness in prehospital settings. BT, body temperature; HR, heart rate; RR, respiratory rate; sBP, systolic blood pressure; SpO₂, oxygen saturation by pulse oximetry.

diagnosis or exclusion for diagnosis, respectively.¹⁷ Statistical analyses were undertaken using JMP version 12 (SAS Institute, Cary, NC, USA).

RESULTS

DURING THE STUDY period, the paramedics measured blood glucose for 1,791 patients; of these, 1,242 patients were included in our final cohort after excluding 549 patients (Fig. 1).

In total, 324 patients (26.1%) had hypoglycemia. Table 2 shows patient characteristics according to the presence or absence of hypoglycemia. Compared with non-hypoglycemic patients, hypoglycemic patients were significantly younger (median age, 73 years [interquartile range (IQR), 62–82] vs. 76 years [IQR, 65–84]; $P < 0.01$).

Two hundred and fifty-three patients were transported to our hospital as non-hypoglycemic (Data S1 and Table S1).

Examination of vital signs of hypoglycemic and non-hypoglycemic patients

There were significant differences in all vital signs between the two groups, and the distribution of each vital sign is shown in Fig. 2. The ROC curves for these vital signs to predict hypoglycemia in patients with impaired consciousness are shown in Fig. 3. The AUCs for each vital sign were calculated, and were 0.61 (95% CI, 0.58–0.64) for sBP, 0.54 (95% CI, 0.51–0.57) for HR, 0.54 (95% CI, 0.51–0.58) for RR, 0.57 (95% CI, 0.54–0.61) for SpO₂, and 0.71 (95% CI, 0.68–0.74) for BT. The SSLRs for each stratified vital sign are shown in Table 3. When sBP was <100 mmHg or BT was $\geq 38^{\circ}\text{C}$, the

Table 3. Stratum-specific likelihood ratio of each vital sign in patients with impaired consciousness

Strata	Number of patients		Positive SSLR (95% CI)
	Hypoglycemia	Non-hypoglycemia	
sBP (mmHg)			
<100	6	146	0.12 (0.05–0.25)
100–119	36	161	0.63 (0.45–0.89)
120–139	79	176	1.27 (1.01–1.60)
140–159	81	166	1.38 (1.10–1.74)
160–179	65	142	1.30 (1.00–1.69)
≥180	57	127	1.27 (0.96–1.69)
HR (/min)			
<60	18	64	0.80 (0.48–1.32)
60–79	125	322	1.10 (0.93–1.29)
80–99	132	294	1.27 (1.08–1.49)
100–119	37	150	0.70 (0.50–0.98)
120–139	10	69	0.41 (0.22–0.78)
≥140	2	19	0.30 (0.08–1.11)
RR (/min)			
<10	0	3	0.00
10–19	134	350	1.08 (0.93–1.26)
20–29	164	446	1.04 (0.92–1.18)
≥30	26	119	0.62 (0.41–0.92)
SpO ₂ (%)			
<90	22	118	0.53 (0.34–0.81)
90–93	39	130	0.85 (0.61–1.19)
94–97	152	436	0.99 (0.86–1.13)
≥98	111	234	1.34 (1.12–1.62)
BT (°C)			
<35.0	36	36	2.83 (1.82–4.40)
35.0–35.9	112	146	2.17 (1.76–2.68)
36.0–36.9	153	489	0.89 (0.78–1.01)
37.0–37.9	18	151	0.34 (0.21–0.54)
≥38.0	5	96	0.15 (0.06–0.35)

BT, body temperature; HR, heart rate; RR, respiratory rate; sBP, systolic blood pressure; SpO₂, oxygen saturation by pulse oximetry; SSLR, stratum-specific likelihood ratio.

SSLR was 0.12 (95% CI, 0.05–0.26) and 0.15 (95% CI, 0.06–0.35), respectively. For those with RR <10/min, the number of patients in the hypoglycemia group was 0, so the SSLR was 0 and the 95% CI could not be measured.

DISCUSSION

THIS RETROSPECTIVE STUDY found that high body temperature and low blood pressure had high predictivity of non-hypoglycemia according to SSLRs in patients with impaired consciousness in prehospital settings.

Considering the association between blood glucose levels and BT, earlier studies have shown that hypoglycemia is associated with hypothermia,¹⁸ which appears to be induced by glucose deficiency in the cells of the hypothalamic center regulating the BT.¹⁹ Our study showed that the higher the BT, the lower the likelihood of hypoglycemia, which suggests that BT might be helpful in considering the possibility of hypoglycemia for patients with impaired consciousness.

Among these vital sign changes, the ROC curve shows that BT has a moderate accuracy in predicting the absence of hypoglycemia in our study. However, if we consider that the threshold value of the Youden index is a BT of 36.2°C, the sensitivity and specificity are not high at 0.65 and 0.67, respectively. Although this value could be an appropriate threshold for the diagnostic accuracy of BT, we considered it more appropriate to use the SSLR for a value that would reduce the likelihood of hypoglycemia being the cause of impaired consciousness. The SSLRs for sBP <100 mmHg and BT ≥38°C were 0.12 and 0.15, respectively. When these vital signs are detected, hypoglycemia is unlikely to be the cause of impaired consciousness. However, it should be noted that the diagnostic accuracy of sBP is low, as shown by the ROC curve. With regards to the association between sBP and impaired consciousness, our findings showed that a low sBP is less likely to be associated with hypoglycemia; thus, this could be a useful indicator for the initial approach to patients with impaired consciousness. Regarding the association between BT and impaired consciousness, a higher BT was associated with infectious diseases such as sepsis in other studies,^{20,21} and these findings are similar to our results.

Early detection and treatment of hypoglycemia are important, and the time involved in measuring blood glucose is short. However, the transport time, the cost of blood glucose measurement, and the burden of paramedics and patients will be reduced if the vital signs could predict non-hypoglycemia. This could be one way of getting the patient the necessary medical attention as quickly as possible.

Evaluating the known risk factors for hypoglycemia, such as a history of diabetes mellitus and renal dysfunction, is useful in predicting its presence.^{22–24} Approximately 69–85% of hypoglycemic patients have a history of diabetes.^{2,25} The findings in this study indicate that hypoglycemia is unlikely but cannot be excluded when patients have vital signs of sBP <100 mmHg and BT ≥38°C. It is important to understand the risk factors for hypoglycemia, but impaired consciousness makes it difficult to obtain clinical information from patients, and approximately 60% of hypoglycemic patients have a confirmed history of diabetes in prehospital settings.⁷ Thus, if vital signs could predict non-hypoglycemia, it will be helpful because vital signs can be

obtained rapidly and easily, even in patients with impaired consciousness.

This study has several limitations. First, there were a number of patients with impaired consciousness who did not receive blood glucose measurements, despite satisfying the criteria for blood glucose measurement; the decision to measure is highly dependent on the paramedic. We could not determine which patients were brought to the hospital without blood glucose measurement. Because brain injuries such as stroke are considered an emergency and are less likely to be associated with hypoglycemia,⁸ blood glucose measurement might not have been carried out if the paramedics suspected such diseases. Second, the possibility of hypoglycemia might not have been adequately assessed by the paramedics with regard to the patients' background, including medical history and medications, which could have influenced the decision to undertake blood glucose measurement. Furthermore, there was a bias in patient selection, although we think that this is a practical consequence of paramedical field activities. Thus, further studies with more cases and in different settings are necessary before changes in recommendations are made.

In conclusion, the presence of high fever or hypotension could be helpful in distinguishing non-hypoglycemia from hypoglycemia in prehospital settings. In particular, BT $\geq 38.0^{\circ}\text{C}$ or sBP < 100 mmHg could identify patients at low risk of hypoglycemia. A validation study using another dataset is needed to confirm the findings in this study.

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DISCLOSURE

Approval of the research protocol: This study was carried out according to the Helsinki Declaration and approved by the ethics board of the Kobe City Medical Centre General Hospital (registration number: zn190919).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Final diagnosis of non-hypoglycemic patients transferred to the Kobe City Medical Centre General Hospital.

Data S1. Details of non-hypoglycemic patients.