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Hypothermia-associated acute pancreatitis: A multicenter prospective observational study

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Abstract

Aim: Hypothermia-associated pancreatitis lacks comprehensive understanding owing to limited studies exploring its mechanism, epidemiology, risk factors, and outcomes. We aimed to investigate the frequency, characteristics, and predictive factors associated with the development of acute pancreatitis in patients with accidental hypothermia.

Methods: This study comprised a post hoc analysis of data from a multicenter prospective observational study (ICE-CRASH study) conducted in 36 tertiary emergency hospitals in Japan. Patients aged ≥18 years with core body temperatures ≤32°C admitted to emergency departments between 2019 and 2022 were enrolled. We identified patients who developed acute pancreatitis within 1 week of admission and described their characteristics. Age, vital signs, and blood gas analysis data were analyzed as potential predictors of acute pancreatitis using receiver operating characteristic (ROC) curve analysis.

Results: Of 421 eligible patients with accidental hypothermia, 16 (3.8%) developed acute pancreatitis within 1 week. The age distribution of patients with acute pancreatitis showed bimodal peaks around 50–80 years. Patients with acute pancreatitis had a higher proportion of alcohol consumption than those without acute pancreatitis. ROC curve analysis showed age and pH as significant factors; however, their predictive power was not high.

Conclusion: The incidence of acute pancreatitis was 3.8% in patients with accidental hypothermia with core body temperatures ≤32°C. An association was found between the development of acute pancreatitis and alcohol consumption. No strong predictors of acute pancreatitis were identified.

KEYWORDS
accidental hypothermia, acute pancreatitis, alcohol-induced pancreatitis, amylase, predictive factor

INTRODUCTION

Accidental hypothermia is defined as a condition in which a person's core body temperature unintentionally decreases below 35°C.[1] This can result from exposure to a cold environment or various underlying medical conditions, such as central nervous system failure, metabolic failure, endocrine failure, and exposure to toxins.[2] The mortality rate of patients with accidental hypothermia has been reported to be as high as 24% based on nationwide Japanese data.[3] In patients with accidental hypothermia, physiological changes throughout the body and reperfusion following rewarming can lead to various complications, including arrhythmias, coagulopathies, electrolyte disorders, and pancreatitis.[1]

Although the occurrence of acute pancreatitis in patients with accidental hypothermia has been reported for a considerable time,[4,5] a comprehensive understanding of its epidemiology, underlying mechanisms, and associated risk factors

remains lacking. Some researchers argue that hypothermia-associated acute pancreatitis may be a misconception, suggesting instead that hypothermia is a consequence, rather than a cause, of acute pancreatitis.[6,7] Regardless of a causal relationship, accurate risk prediction, early detection, and prompt initiation of treatment for acute pancreatitis are crucial for appropriate intensive care management of patients with accidental hypothermia.

In this study, we conducted a post hoc analysis of a multicenter prospective observational study in Japan to investigate the prevalence and characteristics of acute pancreatitis in patients with accidental hypothermia. Additionally, we examined whether any predictive factors for acute pancreatitis could be identified at the time of initial treatment.

MATERIALS AND METHODS

Study design and ethics approval

This was a post hoc analysis of the Intensive Care with Extracorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia (ICE-CRASH) study,[8,9] a multicenter prospective observational study that investigated patients with accidental hypothermia. The ICE-CRASH study was conducted at 36 tertiary care centers in Japan, and data were prospectively collected from December 2019 to March 2022. The protocol for the ICE-CRASH study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN registry No. 00036132) and was approved by the institutional review boards of Asahikawa Medical University (approval No. 18194, date: August 2, 2019) and all relevant institutions. This study was conducted in compliance with the Declaration of Helsinki.

Enrollment of patients in the ICE-CRASH study

The ICE-CRASH study enrolled consecutive patients with accidental hypothermia aged ≥18 years whose core body temperatures fell below 32°C upon emergency department (ED) arrival. Patients with cardiac arrest upon arrival for whom cardiopulmonary resuscitation was not attempted were excluded from the ICE-CRASH study. Data were prospectively collected using an electronic data-capture system. The following data were recorded: age, sex, activities of daily living, the location where the patient was found by the emergency medical service, causes of accidental hypothermia, alcohol consumption underlying accidental hypothermia, vital signs including core body temperature on ED arrival, initial blood gas analysis, initial laboratory data, Sequential Organ Failure Assessment (SOFA) score,[10] information on acute pancreatitis, in-hospital death, and 28-day survival outcomes.

Patient selection

In this study, we excluded patients who either did not achieve a return of spontaneous circulation after experiencing cardiac arrest before admission or were resuscitated but died within 24 h of admission, as these patients were unlikely to have had the chance to undergo a diagnostic evaluation for acute pancreatitis.

Outcome and definitions

The primary outcome of the study was the development of acute pancreatitis within 1 week of admission, including cases where patients presented with acute pancreatitis upon admission. Eligible patients were divided into two groups: those who developed acute pancreatitis (AP group) and those who did not (control group). Acute pancreatitis was diagnosed when at least two of the following criteria were met[11]: (1) acute abdominal pain and tenderness in the upper abdomen; (2) elevated pancreatic enzyme levels in the blood, urine, or ascitic fluid; and (3) abnormal imaging findings in the pancreas indicative of acute pancreatitis. Alcohol consumption was defined as alcohol intake prior to the hypothermic event without regard to regular drinking habits. Patients were then categorized into alcoholic and nonalcoholic subgroups according to this definition.

Statistical analyses

All variables are expressed as medians with interquartile ranges (IQRs) or percentages. Missing values were excluded from the analysis. The predictive ability of initial vital signs and blood gas analysis data for the development of acute pancreatitis was assessed using the area under the receiver operating characteristic (ROC) curve (AUC). Optimal cutoff points were determined from the ROC curves using the Youden index. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated at these cutoff points. To eliminate the influence of alcohol consumption on pancreatitis, analyses were performed on the nonalcoholic subgroup. All statistical analyses were performed using R software version 4.1.2. (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics, acute pancreatitis, and prognosis

Of the 441 patients enrolled in the ICE-CRASH study, 20 were excluded, and the data of 421 eligible patients were analyzed (Figure 1). Table 1 summarizes the demographic and clinical characteristics of the eligible patients. The

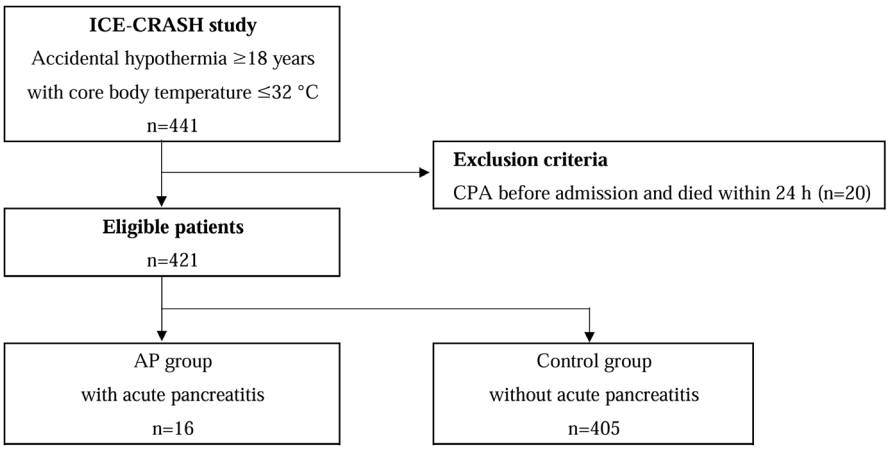

FIGURE 1 Flow chart showing the inclusion and exclusion of participants in this study. CPA, cardiopulmonary arrest.

median core body temperature at admission was 28.5°C (IQR, 27.1–30.2), and the 28-day mortality rate was 20.2%. A total of 16 (3.8%) developed acute pancreatitis within 1 week of admission. When divided according to alcohol consumption, the incidence of acute pancreatitis was 2.0% (6/302) in the nonalcoholic subgroup and 10.0% (5/50) in the alcoholic subgroup. Table 1 shows a comparison between the AP and control groups. Compared with the control group, the AP group exhibited a younger median age, a higher proportion of patients who consumed alcohol, and a lower pH. The AP group also demonstrated higher SOFA scores and increased mortality.

Patients with acute pancreatitis

A summary of the acute pancreatitis cases in this study is presented in Table 2. The age distribution of patients with acute pancreatitis showed bimodal peaks, with one peak around 50–60 years and another around 80 years. Alcohol consumption was more prevalent among the younger group. In most cases, the initial core body temperature upon ED arrival was below 30°C. Many patients had elevated serum amylase and serum lipase levels at admission.

Predictive factors for acute pancreatitis development

Table 3 shows the AUCs of age, vital signs, and blood gas analysis data in predicting acute pancreatitis development based on the first measurements taken in the ED. Age and pH were statistically significant prognostic factors, with AUCs of 0.684 and 0.656, respectively. The ROC curves for each variable are shown in Figure 2. Cutoff values derived from the Youden index and their predictive accuracies are shown in Table 4. Notably, age and systolic blood pressure demonstrated high sensitivity, suggesting that patients older than 83 years or with a systolic blood pressure above 133 mmHg are less likely to have or develop acute pancreatitis. We conducted the same analysis in the nonalcoholic subgroup to minimize the impact of alcohol on pancreatitis; however, with only six cases of acute pancreatitis in this subgroup, the event count was insufficient for reliable ROC curve estimates.[12] For reference, analysis results for the nonalcoholic subgroup are presented in Tables S1 and S2, and Figure S1, indicating that core body temperature and Glasgow Coma Scale were significant factors, with AUCs of 0.723 and 0.728, respectively.

DISCUSSION

To the best of our knowledge, this is the first multicenter prospective observational study to investigate accidental hypothermia. The incidence of acute pancreatitis was 3.8% in all patients, increasing to 10.0% in the alcoholic subgroup. Mortality was higher in patients with acute pancreatitis compared to those without. Although we did not identify strong predictors for the development of acute pancreatitis in patients with accidental hypothermia, our analysis suggested that older patients and those with high blood pressure are less likely to develop acute pancreatitis.

In this study, the incidence of acute pancreatitis was higher in the alcoholic subgroup compared to the nonalcoholic subgroup, suggesting that alcohol may contribute to the development of hypothermia-associated acute pancreatitis. Only one previous observational study has examined acute pancreatitis in patients with accidental hypothermia,[13] reporting an incidence of 8.7% (12/138), more than twice that in our study, likely because of a higher proportion (53%) of alcohol consumers. Patients in the AP group were younger than those in the control group, possibly because of higher rates of alcohol consumption among younger patients. Additionally, higher pancreatic exocrine function in young individuals may contribute to the onset of acute pancreatitis.[14,15] In this study, we defined alcohol consumers as patients who had consumed alcohol immediately before the hypothermic event, and such patients were most likely habitual alcohol users. Habitual alcohol consumption is a known

TABLE 1 Demographic characteristics, clinical data, and outcomes in eligible patients.

	All patients	Missing	Control group	AP group
	n = 421	*n* (%)	*n* = 405	*n* = 16
Age, years	81 [70–88]		81 [71–88]	70 [55–81]
Sex, male	229 (54.4)		221 (54.6)	8 (50.0)
ADL		11 (2.6)		
Independent	244 (58.0)		234 (57.8)	10 (62.5)
Partial dependent	142 (33.7)		140 (34.6)	2 (12.5)
Total dependent	24 (5.7)		21 (5.2)	3 (18.8)
Location		1 (0.2)		
Indoor	327 (77.7)		312 (77.0)	15 (93.8)
Outdoor	93 (22.1)		92 (22.7)	1 (6.2)
Cause of accidental hypothermia				
Infection	82 (19.5)		80 (19.8)	2 (12.5)
Endocrine disease	62 (14.7)		58 (14.3)	4 (25.0)
Cerebrovascular disease	27 (6.4)		26 (6.4)	1 (6.2)
Intoxication	32 (7.6)		30 (7.4)	2 (12.5)
Trauma	29 (6.9)		29 (7.2)	0 (0)
Cardiovascular disease	10 (2.4)		10 (2.5)	0 (0)
Others	91 (21.6)		86 (21.2)	5 (31.2)
Unknown	88 (20.9)		86 (21.2)	2 (12.5)
Alcohol consumption, yes	50 (11.9)	69 (16.4)	45 (11.1)	5 (31.2)
Vital signs on ED arrival				
Glasgow Coma Scale	9.0 [6.0–12.0]		10.0 [6.0–12.0]	7.0 [3.0–11.5]
Heart rate, beat/min	64 [48–82]		65 [49–82]	52 [43–90]
Systolic blood pressure, mmHg	113 [88–139]		114 [88–140]	98 [67–129]
Core body temperature, °C	28.5 [27.1–30.2]		28.6 [27.1–30.2]	27.8 [26.1–28.7]
Initial blood gas analysis				
pH	7.29 [7.17–7.35]	8 (1.9)	7.29 [7.18–7.35]	7.20 [7.04–7.28]
$PaCO_2$, mmHg	41.8 [32.0–52.2]	9 (2.1)	41.8 [32.7–52.4]	33.4 [27.3–45.1]
HCO_3^-, mmol/L	19.8 [14.0–24.7]	9 (2.1)	19.9 [14.2–24.8]	12.6 [6.1–23.8]
Base excess, mmol/L	−6.4 [−12.1–-1.2]	9 (2.1)	−6.4 [−11.8–-1.1]	−13.9 [−22.3–-3.2]
Lactate, mmol/L	2.9 [1.3–6.2]	9 (2.1)	2.8 [1.2–6.1]	4.3 [3.1–7.1]
Initial laboratory data				
White blood cell count, ×1000/μL	9.0 [5.1–14.1]		9.0 [5.2–14.2]	8.4 [4.3–13.1]
Hemoglobin, g/dL	11.6 [9.8–13.7]		11.6 [9.8–13.7]	11.3 [8.1–13.6]
Hematocrit, %	35.3 [30.0–41.4]		35.5 [30.1–41.6]	33.6 [25.4–41.2]
Platelet count, ×1000/μL	171 [112–237]		171 [113–237]	161 [93–204]
Prothrombin time, INR	1.17 [1.03–1.37]	3 (0.7)	1.17 [1.03–1.37]	1.23 [1.09–1.30]
APTT, s	34.5 [30.0–42.0]	5 (1.2)	34.5 [29.9–42.0]	35.4 [32.8–38.5]
FDP, μg/mL	7.4 [4.0–17.7]	191 (45.4)	7.4 [4.0–17.0]	7.7 [4.1–21.7]
D-dimer, μg/mL	3.0 [1.4–7.7]	48 (11.4)	3.0 [1.3–7.7]	3.0 [2.2–7.5]
Antithrombin, %	81 [67–96]	261 (62.0)	81 [67–94]	76 [56–97]
Amylase, U/L	113 [70–240]	57 (13.5)	111 [69–224]	370 [183–1211]
Lipase, U/L	34 [19–88]	333 (79.1)	32 [19–50]	1103 [519–1322]
Total bilirubin, mg/dL	0.7 [0.4–1.1]		0.7 [0.4–1.2]	0.4 [0.4–0.6]
CK, U/L	586 [237–1783]	5 (1.2)	574 [234–1745]	757 [454–2048]

TABLE 1 (Continued)

	All patients	Missing	Control group	AP group
	n = 421	*n* (%)	*n* = 405	*n* = 16
Creatinine, mg/dL	1.2 [0.7–2.1]		1.2 [0.7–2.1]	1.8 [1.0–3.2]
Serum sodium, mmol/L	140 [136–144]		140 [137–144]	137 [129–142]
Serum potassium, mmol/L	4.2 [3.6–4.8]		4.2 [3.6–4.7]	4.2 [3.9–5.0]
Glucose, mg/dL	129 [89–193]	5 (1.2)	129 [89–189]	162 [98–634]
SOFA score on admission day	6 [4–9]		6 [4–9]	10 [4–14]
Development of acute pancreatitis	16 (3.8)		0 (0)	16 (100)
In–hospital death	88 (20.9)		82 (20.2)	6 (37.5)
28-day death	85 (20.2)	19 (4.5)	79 (19.5)	6 (37.5)

Note: All data are presented as medians [interquartile ranges] or *n* (%).

Abbreviations: ADL, activities of daily living; APTT, activated partial thromboplastin time; CK, creatinine kinase; ED, emergency department; FDP, fibrin/fibrinogen degradation products; INR, international normalized ratio; SOFA, Sequential Organ Failure Assessment.

TABLE 2 Case series of patients with acute pancreatitis.

Case	Sex	Age (years)	Cause of accidental hypothermia	Alcohol consumption	Core body temperature (°C)	Serum amylase level (U/L)	Serum lipase level (U/L)	SOFA score on admission day	28-day mortality
1	Male	50–59	Others	No	25.1	184	519	8	Survived
2	Male	20–29	Endocrine disease	No	27.6	417	1103	15	Survived
3	Female	60–69	Endocrine disease	No	28.4	1135	2537	3	Survived
4	Male	90–99	Others	No	25.8	1641	1669	NA	Deceased
5	Male	70–79	Others	Unknown	29.4	322	NA	2	Survived
6	Female	80–89	Others	Unknown	27.3	285	NA	14	Deceased
7	Male	50–59	Intoxication	Yes	26.2	177	NA	15	Survived
8	Male	50–59	Endocrine disease	Unknown	30.5	722	NA	12	Deceased
9	Female	70–79	Intoxication	Yes	25.2	93	NA	9	Survived
10	Female	80–89	Unknown	No	28.3	1689	NA	14	Survived
11	Female	80–89	Others	Unknown	24.9	319	582	17	Deceased
12	Female	80–89	Unknown	Unknown	30.5	27	10	4	Survived
13	Male	60–69	Cerebrovascular disease	Yes	27.9	1471	NA	10	Survived
14	Female	80–89	Endocrine disease	No	27.3	1438	1222	4	Deceased
15	Male	60–69	Infection	Yes	28.4	180	241	14	Deceased
16	Female	40–49	Infection	Yes	31.7	452	1322	2	Survived

Note: Core body temperature, serum amylase level, and serum lipase level represent the initial measurements taken upon arrival.

Abbreviation: SOFA, sequential organ failure assessment.

risk factor for chronic pancreatitis, which in turn increases the risk of acute pancreatitis,[16] potentially acting as a confounding factor in our results.

Although previous studies have reported an increased risk of acute pancreatitis with lower body temperatures,[13] core body temperature was not a significant predictor in the ROC curve analysis in our study. However, in the non-alcoholic subgroup, where alcohol's effect was excluded, core body temperature emerged as a significant factor. Further investigation with a larger sample size is needed to clarify the relationship between alcohol consumption and hypothermia-associated acute pancreatitis.

In the ROC curve analysis conducted in this study, the variables of age, vital signs, and blood gas analysis data each had AUCs below 0.7, indicating low predictive ability.[17] This may be because of multiple contributing factors involved in the development of acute pancreatitis in patients with accidental hypothermia. Proposed mechanisms for hypothermia-associated acute pancreatitis include direct pancreatic injury from hypothermia exposure, circulatory failure because of hypothermia, and alcohol consumption as a contributing factor.[5,18] The exact mechanism by which hypothermia leads to pancreatitis is not fully understood. In a rat model of hypothermia, Inoue et al. demonstrated that histological pancreatic injuries, such as micro-bleeding, occurred when circulatory failure occurred in addition to hypothermia.[18] They also showed that, even without circulatory failure, amylase-stored vacuoles formed within pancreatic acinar cells under hypothermic conditions. Additionally, the metabolic products of ethanol have been reported to induce

pancreatic edema and acinar cell vacuolization,[19] potentially increasing the fragility of vesicles formed during hypothermia and contributing to the onset of pancreatitis.

Patients in the AP group exhibited severe metabolic acidosis. Elevated lactate and serum creatinine levels in this group suggest that renal and circulatory failure may contribute to the observed metabolic acidosis. However, it remains unclear whether metabolic acidosis is a cause or a consequence of acute pancreatitis. Several studies have documented a direct relationship between acidemia and pancreatitis.[20,21] Alternatively, pancreatitis may be more likely to occur in severely ill patients who have metabolic acidosis because of renal failure or lactic acidosis from circulatory failure. As shown in Table 4, clinicians should note that low base excess and bicarbonate ion levels increase the likelihood of acute pancreatitis complications and should not delay evaluation.

This study had some limitations. First, we only had data on acute pancreatitis diagnosis within 1 week of presentation. However, when and how pancreatitis was diagnosed remains unclear. Appropriate blood or imaging tests may not have been performed in all included patients, and pancreatitis may have been missed. Second, as the severity of pancreatitis was not assessed in this study, we could not examine whether disease severity varied with body temperature. Similarly, the relationship between the severity of pancreatitis and prognosis remains unclear. Third, we did not investigate the quantity or habitual pattern of alcohol consumption. Fourth, laboratory data were collected only on admission, and changes in values after hospitalization were not analyzed. Fifth, because of the small number of patients with acute pancreatitis, the results of the ROC curve analysis had wide confidence intervals, which made it difficult to accurately estimate the true values. Lastly, this study did not investigate the underlying causes of hypothermia-associated acute pancreatitis, so it cannot be ruled out that some patients may have developed pancreatitis prior to hypothermia, independent of low body temperature. Additionally, underlying comorbidities in patients with hypothermia may have influenced the development of pancreatitis. Further large prospective studies are needed to address these unresolved issues, focusing on the timing and methods of pancreatitis diagnosis, treatment approaches, clinical course, and detailed information regarding alcohol consumption.

TABLE 3 AUCs of each variable predicting the development of acute pancreatitis.

Variable	AUC [95% Confidence interval]
Age (year)	0.684 [0.557–0.811]
Vital signs	
Glasgow coma scale	0.586 [0.415–0.757]
Heart rate	0.560 [0.374–0.745]
Systolic blood pressure	0.642 [0.481–0.802]
Core body temperature	0.607 [0.465–0.750]
Blood gas analysis	
pH	0.656 [0.515–0.798]
$PaCO_2$	0.605 [0.438–0.772]
HCO_3^-	0.642 [0.470–0.814]
Base excess	0.642 [0.475–0.810]
Lactate	0.632 [0.497–0.767]

Abbreviation: AUC, area under the receiver operating characteristic curve.

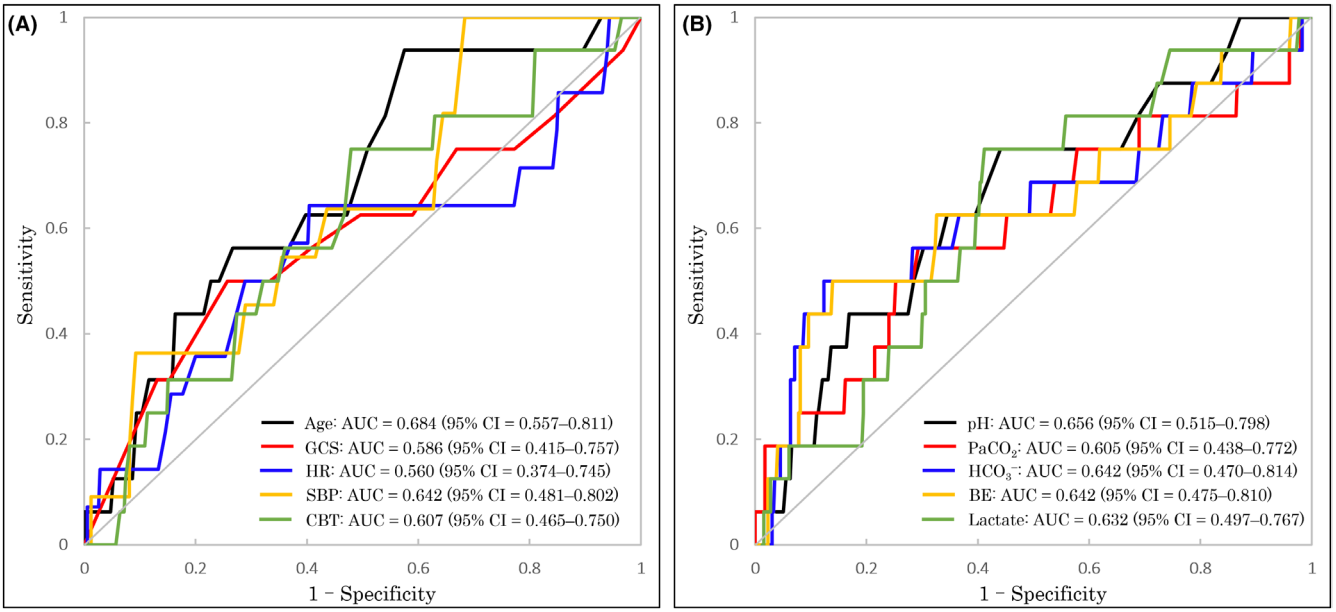

FIGURE 2 Receiver operating characteristic curves for the development of acute pancreatitis. A: Analysis of age and initial vital signs. B: Analysis of initial blood gas analysis data. AUC, area under the curve; BE, base excess; CBT, core body temperature; CI, confidence interval; GCS, Glasgow Coma Scale; HR, heart rate; SBP, systolic blood pressure.

TABLE 4 Predictive performance of variables for development of acute pancreatitis.

Variable	Cutoff value	Sensitivity	Specificity	PPV	NPV	LR+	LR−
Age, years	83	0.938 (0.698–0.998)	0.425 (0.376–0.474)	0.060 (0.034–0.098)	0.994 (0.968–1.000)	1.630 (1.400–1.896)	0.147 (0.022–0.985)
Vital signs							
Glasgow Coma Scale	6	0.500 (0.247–0.753)	0.743 (0.698–0.785)	0.071 (0.031–0.136)	0.974 (0.950–0.989)	1.947 (1.161–3.266)	0.673 (0.411–1.102)
Heart rate, beat/min	57	0.643 (0.351–0.872)	0.596 (0.545–0.645)	0.054 (0.025–0.100)	0.979 (0.952–0.993)	1.591 (1.057–2.394)	0.599 (0.295–1.216)
Systolic blood pressure, mmHg	133	1.000 (0.615–1.000)	0.316 (0.267–0.369)	0.046 (0.023–0.081)	1.000 (0.949–1.000)	1.463 (1.360–1.573)	0.000 (0.000–N/A)
Core body temperature, °C	28.4	0.750 (0.476–0.927)	0.521 (0.471–0.571)	0.058 (0.030–0.100)	0.981 (0.953–0.995)	1.566 (1.159–2.115)	0.480 (0.204–1.127)
Blood gas analysis							
pH	7.270	0.750 (0.476–0.927)	0.559 (0.509–0.809)	0.064 (0.034–0.109)	0.982 (0.955–0.995)	1.701 (1.256–2.305)	0.447 (0.190–1.049)
$PaCO_2$, mmHg	34.0	0.562 (0.299–0.802)	0.707 (0.660–0.751)	0.072 (0.033–0.132)	0.976 (0.950–0.990)	1.920 (1.214–3.037)	0.619 (0.354–1.082)
HCO_3^-, mmol/L	10.2	0.500 (0.247–0.753)	0.876 (0.840–0.907)	0.140 (0.063–0.258)	0.977 (0.956–0.990)	4.041 (2.318–7.044)	0.571 (0.349–0.933)
Base excess, mmol/L	−17.9	0.500 (0.247–0.753)	0.861 (0.823–0.894)	0.127 (0.056–0.235)	0.977 (0.955–0.990)	3.600 (2.081–6.227)	0.581 (0.355–0.949)
Lactate, mmol/L	3.3	0.750 (0.476–0.927)	0.581 (0.530–0.630)	0.067 (0.035–0.115)	0.983 (0.957–0.995)	1.789 (1.318–2.429)	0.430 (0.183–1.010)

Note: Values in parentheses indicate the 95% confidence interval. For lactate, a result is considered positive if it meets or exceeds the cutoff value. For other variables, a result is considered positive if it is at or below the cutoff value. N/A indicates values that could not be calculated.

Abbreviations: LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

CONCLUSION

In our study, the incidence of acute pancreatitis was 3.8% among patients with accidental hypothermia with core body temperatures ≤32°C. Patients with a history of alcohol consumption before hypothermia had a higher incidence of acute pancreatitis. No strong predictors of acute pancreatitis were identified.

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CONFLICT OF INTEREST STATEMENT

Authors declare no Conflict of Interests for this article.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol: This study was approved by the institutional review boards of Asahikawa Medical University (approval No. 18194, date: August 2, 2019).

All relevant institutions, and the requirement for written informed consent was waived because of data anonymity.

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Animal Studies: N/A.

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SUPPORTING INFORMATION

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

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