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Original Contribution

Risk factors for acute pancreatitis in patients with accidental hypothermia

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A B S T R A C T

Background: Pancreatic damage is commonly observed as a consequence of accidental hypothermia (core body temperature below 35 °C). We aimed to investigate the risk factors for pancreatic damage and the causal relationship in patients with accidental hypothermia.
Methods: This retrospective, single-center, observational case-control study was conducted in the emergency department of a tertiary care medical center. We investigated patients who were admitted for accidental hypothermia over a course of ten years (January 2008 to December 2017).
Results: Of the 138 enrolled patients, 70 had elevated serum amylase levels (51%). We observed a correlation between initial core body temperature and serum amylase level (Spearman's rank correlation coefficient −0.302, $p < 0.001$). Patients who developed acute pancreatitis had a significantly lower initial core body temperature than those who did not develop it (odds ratio = 0.76; 95% confidence interval [CI] = 0.61–0.94; $p = 0.011$). Receiver operating characteristic analysis showed that a body temperature lower than 28.5 °C at the time of visit was predictive of acute pancreatitis (area under the curve = 0.71, 95% CI = 0.54–0.88, sensitivity = 0.67, specificity = 0.69, $p = 0.017$).
Conclusions: We concluded that an initial core body temperature lower than 28.5 °C was a risk factor for acute pancreatitis in accidental hypothermia cases. In such situations, careful follow-up is necessary.

1. Introduction

Accidental hypothermia occurs when a person is exposed to low-temperature environments and his/her core temperature drops to lower than 35 °C [1]. Several reports have focused on the relationship between accidental hypothermia and acute pancreatic injury [2,3], and half of all accidental hypothermia patients were found to have elevated serum amylase levels [4]. Additionally, the degree of acute pancreatitis can be severe; therefore, early diagnosis and appropriate treatment are necessary. However, no studies have investigated the risk factors for acute pancreatitis due to accidental hypothermia. Identifying risk factors that can be judged at the time of arrival can aid in delivering appropriate and timely care to patients with accidental hypothermia.

The purpose of the present study was to investigate the frequency of the occurrence of acute pancreatitis and the correlation between hyperamylasemia and acute pancreatitis in cases of accidental hypothermia, and to prove the causal relationship between them. We also examined the simple risk factors associated with acute pancreatitis.

2. Materials and methods

2.1. Study design and setting

This was a retrospective, single-center, observational case-control study. We enrolled 180 patients who were admitted for accidental hypothermia from January 2008 to December 2017. We presented a case series of acute pancreatitis and carried out descriptive statistics. The study protocol was approved by the institutional review board of the hospital, and the participants provided written consent. All study procedures were carried out in accordance with the Declaration of Helsinki.

2.2. Study protocol and data collection

The criterion for inclusion in this study was having a body temperature lower than 35 °C on arrival at the emergency department. Patients who had an out-of-hospital cardiac arrest (considering the influence of a cessation in circulation on the pancreas) or those for whom there were no data on serum amylase levels were excluded from the analysis. The primary outcome was acute pancreatitis, and the secondary outcome was serum amylase level.

For the diagnosis and severity stratification of acute pancreatitis, the Japanese criteria formulated by the Research Committee of Intractable Diseases of the Pancreas in Japan (JPN diagnostic criteria 2008) were

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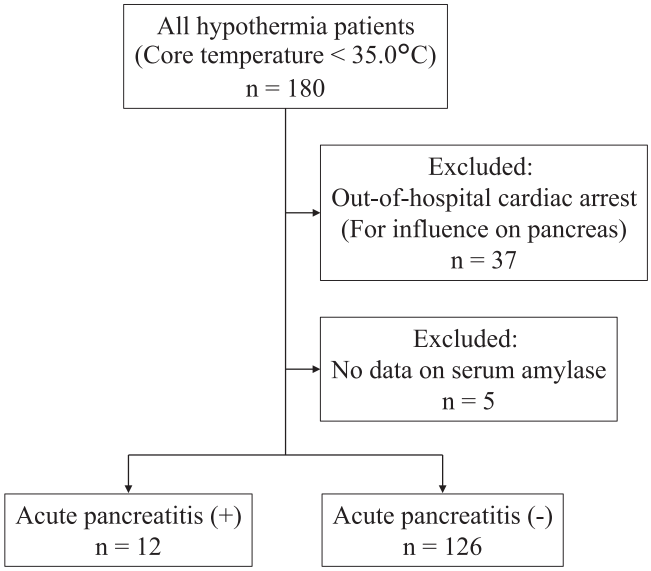

Fig. 1. Flow chart of patient selection by inclusion and exclusion criteria.

used [5]. The clinical criteria for the diagnosis of acute pancreatitis are: (1) acute pain and tenderness in the upper abdomen; (2) elevated pancreatic enzyme levels in blood and/or urine; and (3) ultrasound, computed tomography (CT) or magnetic resonance imaging abnormalities of the pancreas that are characteristic of acute pancreatitis. When at least two of the above conditions are present, the diagnosis of acute pancreatitis can be confirmed. We referenced the chart and collected data accordingly.

2.3. Statistical analysis

Spearman's rank correlation analysis was performed to examine the relationship between initial body core temperature and serum amylase levels, and between initial systolic blood pressure and serum amylase levels. The background characteristics of the acute pancreatitis and the non-acute pancreatitis groups were compared using the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables.

Multivariate logistic regression analysis was used to explore the exact association between acute pancreatitis and initial body core temperature, with potential predictors as the primary outcome variable. Receiver operating characteristic (ROC) curve analyses were performed to evaluate the body core temperature for the prediction of acute pancreatitis.

All reported p values were two-tailed, and values < 0.05 were considered statistically significant. With a standard deviation of 2.76 and an alpha of 0.05, we found a sample size of 147 patients would be required to detect such a difference with 80% power. All statistical analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 25.0 (IBM Corp, Armonk, NY, USA).

3. Results

A total of 180 patients were diagnosed with accidental hypothermia during the study term. Cases were excluded if cardiac arrest occurred before arrival at the hospital (n = 37), and if data on serum amylase levels at admission were not available (n = 5). A total of 138 patients (72 male and 66 female patients), aged between 20 and 96 years (mean, 65.6 years), were selected for analysis. Of the 138 patients, 12 had acute pancreatitis (Fig. 1), and 70 (51%) had elevated serum amylase levels. Details of the 12 acute pancreatitis cases, including the cause of hypothermia and the severity, are shown in Table 1. Fig. 2 shows a contrast-enhanced CT image of a patient with severe acute pancreatitis (Case No. 1).

We investigated the correlation between initial body core temperature and peak serum amylase level using Spearman's rank correlation analysis (Fig. 3). Spearman's rank correlation coefficient (Rs) was −0.302 (p < 0.001). In addition, we investigated the correlation between initial systolic blood pressure and peak serum amylase level. Spearman's rank correlation coefficient (Rs) was −0.206 (p = 0.024). This result demonstrates that as the body core temperature reduces, the amylase levels and incidences of pancreatitis increase. There was almost no correlation between blood pressure and amylase.

Based on the presence or absence of pancreatitis, participants were divided into two groups, and their background characteristics were statistically examined (Table 2). We observed a significant difference between groups in terms of initial core body temperature, systolic blood pressure, initial serum amylase, peak serum amylase, serum lipase levels, and length of hospital stay.

As alcohol consumption is reported to be a risk factor for acute pancreatitis, multivariate logistic regression analysis was performed by adding the presence of drinking alcohol to the explanatory variables [6]. Patients who developed acute pancreatitis had a significantly lower initial core body temperature than those who did not (odds ratio = 0.76; 95% confidence interval [CI] = 0.61–0.94; p = 0.011).

ROC curves were used to investigate the predictive power of acute pancreatitis in evaluating initial core body temperature (Fig. 4). The cutoff threshold was 28.5 °C (area under the curve [AUC] = 0.71, 95% CI = 0.54–0.88, sensitivity = 0.67, specificity = 0.69, p = 0.017). Assuming that an initial core body temperature 28.5 °C is a risk factor, the relative risk ratio was 3.87, 95% CI = 1.229–12.198 (p = 0.030).

Table 1
A case series of 12 patients with acute pancreatitis caused by accidental hypothermia.

No.	Age, years	Sex	Initial core temperature, °C	Cause of hypothermia	Severity of pancreatitis	Initial serum amylase, U/L	Peak serum amylase, U/L	Drinking	Smoking	Outcome
1	29	Male	28.5	Hyperglycemia	Severe	674	674	+	−	Cure
2	54	Male	25.0	Alcoholism	Severe	969	969	+	N/A	Cure
3	60	Female	25.4	Suicide	Mild	409	409	+	−	Cure
4	82	Male	31.3	Dementia	Mild	125	529	+	+	Death
5	76	Female	26.9	Hyponatremia	Mild	1420	1965	−	−	Cure
6	89	Male	24.6	Hypoglycemia	Severe	518	580	−	−	Cure
7	92	Male	23.5	Accident	Severe	224	566	−	−	Cure
8	68	Female	29.0	Suicide	Mild	641	641	−	+	Cure
9	89	Female	30.5	Dementia	Severe	458	458	−	+	Cure
10	48	Female	27.8	Suicide	Severe	1124	1675	+	−	Cure
11	79	Female	32.7	Weakness	Mild	1536	2790	−	−	Cure
12	68	Female	24.4	Suicide	Severe	344	419	−	−	Cure

Reference range, serum amylase level, 37–120 U/L.
N/A, not available.

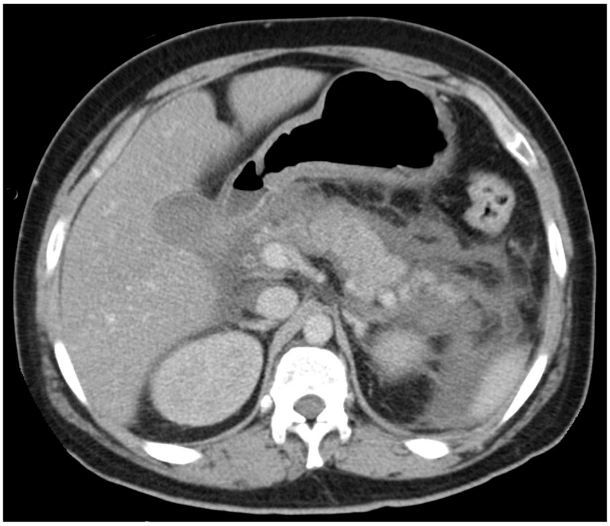

Fig. 2. Enhanced computed tomography image of severe acute pancreatitis caused by accidental hypothermia.

4. Discussion

The purpose of this study was to investigate the causal relationship in patients with accidental hypothermia and to investigate the risk factors for pancreatic damage. A causal relationship was proved through the correlation between serum amylase levels and body temperatures, and a risk factor was identified that is quick and convenient to assess.

In this study, a rise in serum amylase levels was confirmed in about 50% of participants, as observed in another study [4]. Although one study reported that hypothermia was not a clinically-relevant risk factor for acute pancreatitis [7], we used Japanese diagnostic criteria [5], which are almost the same as the Atlanta diagnostic criteria [8]. Acute pancreatitis was recognized in about 10% of the participants in this study. This finding confirms the results of a previous study, in which acute pancreatitis was observed in 20 to 30% of accidental hypothermia autopsy cases [9]. Thus, patients with accidental hypothermia do seem to experience pancreatic injuries such as hyperamylasemia or acute pancreatitis. According to Spearman's rank correlation analysis, as the body temperature decreases, the serum amylase level rises; this suggests that microscopic injuries to the pancreas occur at a higher rate as hypothermia advances. Therefore, it can be inferred that the risk of acute pancreatitis rises with decreasing body temperature.

However, when 12 cases with acute pancreatitis were summarized as a case series, there were no obvious tendencies observed from evaluating the causes of hypothermia, the severity, and prognosis. Therefore, we decided to explore the risk factors of pancreatic damage by a case control study.

When patients were divided into two groups based on the presence or absence of acute pancreatitis, it became clear that core body temperature and systolic blood pressure on hospital arrival was a risk factor for the onset of acute pancreatitis. However, based on the results of Spearman's correlation coefficient, the causal relationship between blood pressure and pancreatic injury was considerably lower than that of body temperature, which supports the finding of core body temperature as the most important risk factor for pancreatitis. Furthermore, the cut-off value obtained in the ROC curve analysis was 28.5 °C, and relative risk revealed that patients with a body temperature lower than 28.5 °C were 3.87 times more likely to experience acute pancreatitis than were patients with a body temperature higher than 28.5 °C.

Alcohol consumption and obesity are reported to be risk factors for acute pancreatitis [6,10-12], but in this study we found no corresponding differences in the presence or absence of acute pancreatitis in accidental hypothermia patients; a low body temperature was the only independent risk.

The mortality associated with acute pancreatitis is 2.1 to 7.8%, making it a very severe disease [13-15]. This study's findings enable the careful follow-up and early diagnosis of acute pancreatitis, especially in this high-risk group; therefore, the deterioration of prognoses can be prevented through early treatment intervention. In other words, when the core body temperature is lower than 28.5 °C at the time of arrival, an evaluation of abdominal findings, measurement of serum amylase levels, and abdominal contrast-enhanced CT should be performed. As acute pancreatitis is a reported complication associated with brain hypothermia therapy for various diseases or injuries [16-17], this finding supports the need for clinical consideration of pancreatic damage caused by hypothermia therapy.

This study clarified the association between hypothermia and pancreatic injury. However, the underlying mechanisms, such circulatory disorders developing due to a decline in the pancreatic temperature, pancreatic ischemia due to microthrombosis, or damage due to serum cytokine level elevation, have not yet been elucidated [18-20]. Alcohol is known as the most common cause of acute pancreatitis, and its mechanism is thought to be related to sphincter of Oddi dysfunction, occlusion of the pancreatic conduit from precipitation of insoluble protein

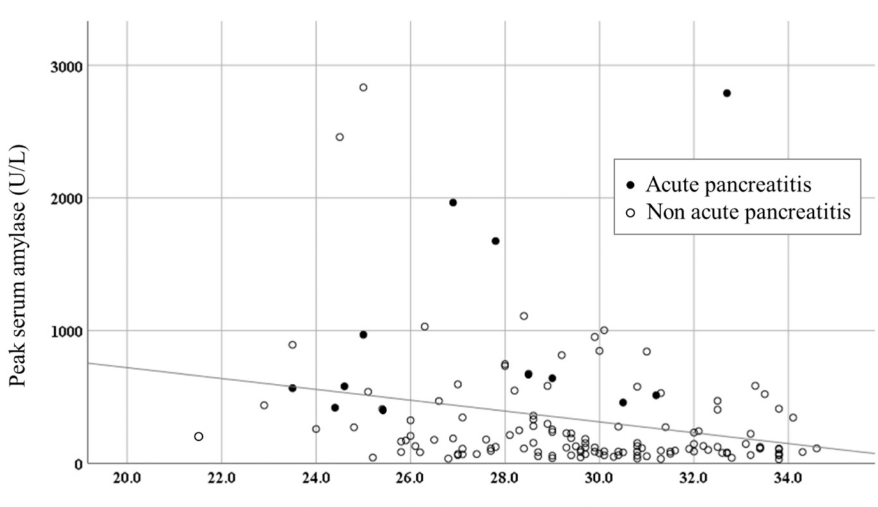

Fig. 3. Correlation between initial core body temperature and peak serum amylase.

Table 2
Background characteristics of the acute pancreatitis group and the non-acute pancreatitis group.

Variable	All patients (n = 138)	Acute pancreatitis (+) (n = 12)	Acute pancreatitis (−) (n = 126)	p value
Age	68 (51–81)	72.00 (59–84)	68 (51–80)	0.41
Male sex, n	72 (52%)	5 (42%)	67 (53%)	0.55
Body mass index (kg/m^2)	20.8 (19.1–23.7)	20.1 (18.7–22.5)	20.8 (19.2–23.8)	0.59
Drinking habit, n	60 (53%)	5 (42%)	55 (55%)	0.54
Smoking habit, n	51 (51%)	3 (27%)	48 (54%)	0.12
Initial core body temperature (°C)	29.6 (27.6–31.5)	27.4 (24.9–29.4)	29.7 (27.9–31.8)	0.017
Winter season (November–April), n	109 (79%)	7 (58%)	102 (81%)	0.13
Glasgow Coma Scale	8 (6–11)	6 (5–9)	8 (6–12)	0.084
Respiratory rate (breaths per minute)	16 (14–22)	16 (10−21)	16 (14–22)	0.5
SpO_2	100 (98–100)	100 (99–100)	100 (98–100)	0.89
Heart rate (beats per minute)	70 (58–91)	51.5 (40–93)	72 (60–90)	0.21
Systolic blood pressure (mm Hg)	120 (93–142)	92 (85–113)	122 (94–143)	0.033
Diastolic blood pressure (mm Hg)	70 (54–91)	65 (50–75)	70 (54–93)	0.3
Arterial blood gas analysis				
pH	7.26 (7.15–7.33)	7.28 (7.13–7.32)	7.26 (7.16–7.33)	0.87
PaO_2 (mm Hg)	214 (105–336)	282 (143–369)	210 (105–331)	0.28
$PaCO_2$ (mm Hg)	43 (34–52)	39 (27–58)	43 (35–50)	0.63
Lactate (mmol/L)	4.7 (2.8–9.2)	5.5 (3.1–6.7)	4.7 (2.8–9.3)	0.94
Initial serum amylase (U/L)	102 (63–247)	580 (393–1008)	95 (60–185)	<0.001
Peak serum amylase (U/L)	149 (85–411)	611 (511–1146)	126 (83–279)	<0.001
Upward trend in serum amylase, n	70 (51%)	7 (58%)	63 (50%)	0.76
Serum lipase (U/L)	78 (15–421)	539 (421–1063)	15 (7.4–49)	0.008
Length of hospital stay (days)	6 (3−13)	11 (8–15)	5 (2−12)	0.024
Discharge destination, n				0.74
Home	38 (28%)	2 (17%)	36 (29%)	
Hospital transfer	83 (60%)	9 (75%)	74 (59%)	
Death	17 (12%)	1 (8.3%)	16 (13%)	

Continuous variables are presented as median with interquartile range (IQR).
Reference range, serum lipase level, 8.7–48 U/L.

plugs, or activation of pancreatic protease. Gene mutation and smoking have also been reported as cofactors that can cause pancreatitis [21]. Thus, the mechanisms of alcoholic pancreatitis and hypothermic pancreatitis are usually different, and it is difficult to use alcoholic pancreatitis as a clue for investigating the mechanism of hypothermic pancreatitis. Some reports suggest that hypothermia may cause microinfarction not only in the pancreas but also in the gut, liver, brain, myocardium, and many other organs [22-23], and that pancreatitis and rhabdomyolysis occurred most frequently as complications during therapeutic hypothermia after cardiopulmonary arrest [24]. Therefore, investigating hypothermia's effects on organs other than the pancreas may help elucidate the mechanism of pancreatic damage caused by hypothermia. If the mechanism is better understood, it can be used in prevention and treatment, and we are currently performing experiments using animal models of hypothermia to achieve this goal.

No study to date has verified the correlation between body temperature and the onset of acute pancreatitis; to the best of our knowledge, this is the first study to do so, and our findings are novel. However, this study has several limitations. First, it is a single-center retrospective observational study, and not all confounding factors could be removed. Second, the sample size of 138 cases (with 12 pancreatitis cases) was slightly small, with a power of 74%. A large sample size may show significant differences in other factors, and future multicenter investigations with larger sample sizes are required. Third, our facility is a tertiary emergency medical hospital with only seriously ill patients, and so only patients with severe disease and poor vital signs among all accidental hypothermia cases are transported here. As a result, the circulatory dynamics of these patients are often deteriorated, which may affect the pancreas. However, because acute pancreatitis rarely occurs in cases of mild hypothermia, studying a population with severe hypothermia is relevant.

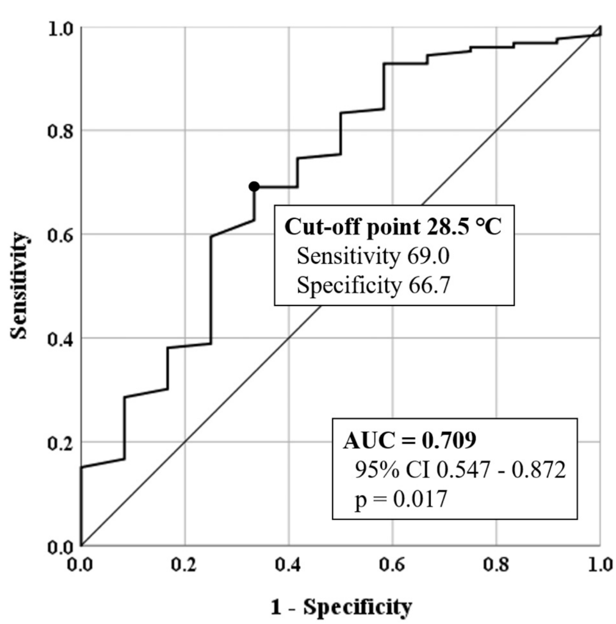

Fig. 4. ROC curve for the prediction of the initial core body temperature that is likely to cause acute pancreatitis. AUC, area under the curve; CI, confidence interval; ROC, receiver operating curve.

5. Conclusions

We have summarized a case series of accidental hypothermia with acute pancreatitis. The observed correlation between serum amylase levels and acute pancreatitis revealed a causal relationship between accidental hypothermia and pancreatic injuries, such as acute pancreatitis. A key risk factor for acute pancreatitis in accidental hypothermia cases is the core body temperature, with the risk of acute pancreatitis rising when the initial core body temperature falls below 28.5 °C.

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Declarations of interest

None.

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