Pancreatology 20 (2020) 307–317

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original Article

# Etiology and mortality in severe acute pancreatitis: A multicenter study in Japan

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https://doi.org/10.1016/j.pan.2020.03.001

ARTICLE INFO

*Article history:*
Received 19 November 2019
Received in revised form
20 February 2020
Accepted 4 March 2020
Available online 6 March 2020

*Keywords:*
Decision-tree model
Epidemiology
Pancreatic infection
Pancreas inflammation
Prognosis

ABSTRACT

*Background/Objectives:* Severe acute pancreatitis (SAP) has a high mortality rate despite ongoing attempts to improve prognosis through a various therapeutic modalities. This study aimed to delineate etiology-based routes that may guide clinical decisions for the treatment of SAP.
*Methods:* Using data from a recent retrospective multicenter study in Japan, we analyzed the association between clinical outcomes, mainly in-hospital mortality and pancreatic infection, and various etiologies while considering confounding factors. We performed additional multivariate analyses and built decision tree models.
*Results:* The 1097 participating patients were classified into the following groups by etiology: alcohol (n = 436, 39.7%); cholelithiasis (n = 230, 21.0%); idiopathic (n = 227, 20.7%); and others (n = 204, 18.6%). Mortality at hospital discharge was 8.4%, 12.2%, 16.7%, and 16.2% in the alcohol, cholelithiasis, idiopathic, and others groups, respectively. According to multivariable analysis, early enteral nutrition (EN) was significantly associated with reduced in-hospital mortality only in the cholelithiasis group. However, there was a consistent association between age and the need for mechanical ventilation and increased mortality, regardless of etiology. Our decision tree models presented different contributing factors depending on the etiology and patient background. Interaction analysis showed that EN and the use of prophylactic antibiotics may influence these results differently according to etiology.
*Conclusions:* No study has yet used comprehensive models to investigate etiology-related prognostic factors for SAP; our results can, therefore, be used as a reference for improving clinical decisions.


## Introduction

Acute pancreatitis (AP) is an inflammatory disease involving autodigestion of the pancreas with an annual incidence of 20–80 per 100,000 individuals. Patients are primarily middle-aged and elderly males, and the incidence is on the rise worldwide [1,2]. Although the pathophysiology of AP is not completely understood, one proposed mechanism is that activation of early intra-acinar nuclear factor kappa B (NF-kB) in addition to the activation of pancreatic enzymes (trypsinogen) may be crucial [3]. AP can rapidly advance to severe acute pancreatitis (SAP) (15%–26% cases), which is associated with multisystem organ failure, high financial burdens, and high mortality rates [1,2,4]. Depending on the country and the quality of the intensive care [5], in-hospital mortality rates of SAP are estimated to be 5%–42% [1,2,4,6]. Effective clinical management is crucial because of the poor prognosis of SAP, resulting in the creation of several guidelines and various prognostic scores [4,7–10]. Invasive interventions and treatments for SAP include mechanical ventilation, continuous renal replacement therapy, administration of protease inhibitors, infusion of large volumes of fluid, enteral and parenteral nutrition, prophylactic antibiotics, and surgical removal of necrotizing tissue [2,5,10,11]. Nonetheless, the influence of various treatments on the prognosis of SAP patients remains unclear because contradictory conclusions have to be drawn from different studies.

The most common causes of AP are cholelithiasis (gallstones) and alcoholism, followed by idiopathic cases, complications of endoscopic retrograde cholangiopancreatography (ERCP), hypertriglyceridemia, pancreatic cancer, and hypercalcemia [1,2]. The etiological causes of AP along with various confounding factors for mortality and infection may play an important role in the differences in mortality and pancreatic infection rates in patients with SAP. Previous studies using the SAP database showed that the cause of mortality in SAP was different across the various etiologies [12,13]. However, these epidemiological SAP studies have collected data on patient background, morbidity, and mode of treatment, but they have failed to use this data to devise better evidence-based practice policies. Although previous studies have shown that the mortality and infection rates of SAP patients differ according to etiology, it has been suggested that the ultimate clinical outcome may depend on a complex interaction between multiple confounding factors, such as age and etiological causes. The confounding factors that affect mortality and pancreatic infection may possibly differ between etiologies of SAP. However, no studies thus far have examined differences in outcomes, such as mortality and pancreatic infection, between etiologies using multivariable analysis to compare differences in the effect of confounding factors on outcomes.

We have previously conducted a retrospective multicenter study conducted in Japan in which more than 1000 SAP patients were enrolled and evaluated [14]. We classified patients into 4 etiological categories (alcohol, cholelithiasis, idiopathic, and others), considered the possible confounding factors, and performed post-hoc analysis on the data. The major clinical outcomes were in-hospital mortality and pancreatic infection. Our aim was to delineate etiology-based routes that may be used as a reference for making clinical decisions for the treatment of SAP.

## Methods

### *Study design and patients*

This post-hoc analysis study included data from a multicenter retrospective study across 44 institutions in Japan, in which 1159 patients were diagnosed with SAP (2009–2013) [14]. The study was registered at the University Hospital Medical Information Network Clinical Trials Registry (Registry number: 000012220) and was approved by the Institutional Review Board or Medical Ethics Committee of each institution. It was reported in accordance with the Strengthening Reporting of Observational Studies in Epidemiology guidelines [15]. The original retrospective study evaluated the efficacy of continuous regional arterial infusion in treating SAP(14); however, here, we report further post-hoc analyses on the same data [16–20].

Patient inclusion criteria were being of at least 18 years of age, a diagnosis of SAP, and admission to a hospital regardless of intensive care unit (ICU) status. AP was diagnosed when the patient presented at least 2 of the following 3 clinical findings [1]: acute pain and tenderness in the upper abdomen [2]; elevated pancreatic enzyme levels in the blood and urine [3]; detection of AP by

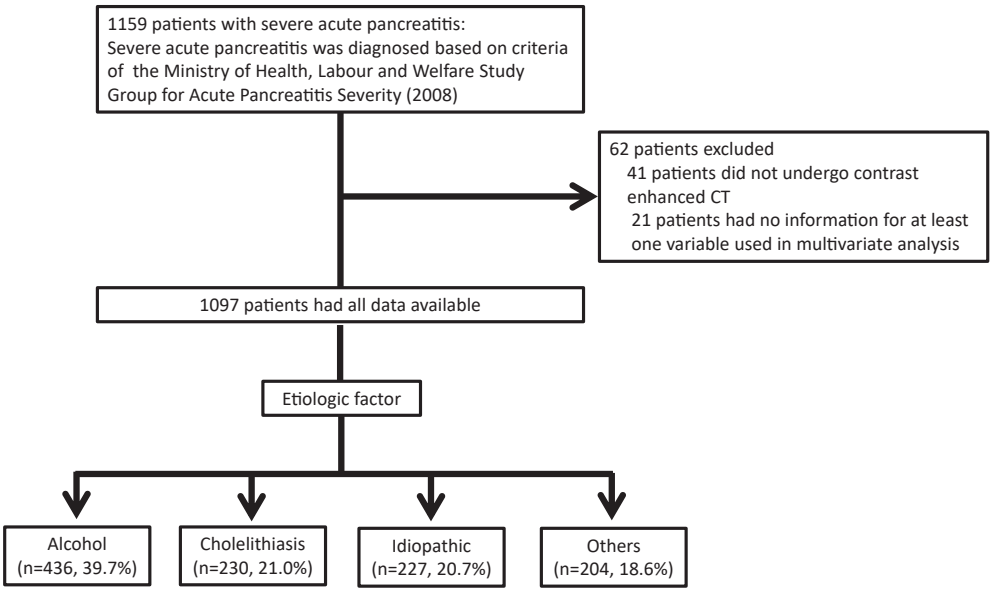



**Fig. 1.** Patient flowchart.

ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI). The diagnosis of SAP was based the Japanese Ministry of Health, Labor, and Welfare (Japanese Severity Score) criteria [4,10] (S-Table 1). This study had no exclusion criteria.

*Data collection and outcomes*

Data, including patient age, sex, etiology of AP, acute physiological parameters, and the following prognostic scores were collected retrospectively [4,7–9,14]: 1) Acute Physiology and Chronic Health Evaluation II (APACHE II) score; 2) CT severity index (CTSI); 3) Charlson comorbidity index; and 4) Severity grade under the revised Atlanta classification. AP was classified into the following 4 etiological categories: alcohol, cholelithiasis, idiopathic, or others. The "others" category included all less frequent etiologies, such as hypertriglyceridemia and post ERCP. The classification of SAP patients into the 4 etiological categories depended on each facility. Post-diagnosis treatments included intravenous fluid administration within 24 h, administration of enteral nutrition (EN) within 48 h, dialysis due to renal failure, use of mechanical ventilator, administration of prophylactic antibiotics, and continuous regional arterial infusion (CRAI) of protease inhibitors. If SAP-diagnosed patients were transferred from another hospital, we collected patient data from the time of arrival. The primary outcome was in-hospital mortality in each etiology. The secondary outcome was pancreatic infection in each etiology.

*Statistical analysis*

Demographic data are presented as means with standard deviation (SD) or medians with interquartile range for continuous variables and as percentages for categorical variables. One-way analysis of variance (ANOVA), Kruskal–Wallis test, or chi-square test with Fisher's exact test was used for comparison, as appropriate. Additionally, multiple pairwise comparisons were performed between etiologies using a multiple comparison test (Bonferroni method). The unadjusted associations between each variable and outcome or etiology were first examined using chi-square test or Mann–Whitney *U* test, as appropriate. Next, a multivariable logistic regression model was adjusted in each group for seven potential confounders that were selected based on *a priori* clinical knowledge—age, revised Atlanta classification, use of renal replacement therapy (RRT), use of ventilator, EN within 48 h, CRAI, and use of prophylactic antibiotics. Interactions were tested and subgroup analysis was performed to assess which factors were significant. Additionally, decision tree models were built to extract the weights of the clinical outcomes with respect to various causes and factors. We conducted further classification and regression tree analyses using the recursive partitioning method with 10 variables, most of which were considered confounding factors—use of ventilator, use of RRT, age, APACHE II score, CRAI, EN within 48 h, Charlson index, use of prophylactic antibiotics, revised Atlanta classification, and CTSI. Patients with missing data were excluded in the final analysis. We did not perform sensitivity analysis. Statistical analyses were performed using JMP 13.0 software (SAS Institute, Cary, NC, USA) and SAS version 9.4 (SAS Inc, Cary, NC); all tests were 2-tailed and a p-value <0.05 was considered statistically significant.

## Results

*Etiology of acute pancreatitis*

Of the 1159 patients diagnosed with SAP [4,10], 62 were excluded because of insufficient data. The remaining 1097 patients were classified into the following groups by etiology: alcohol (n = 436, 39.7%); cholelithiasis (n = 230, 21.0%); idiopathic (n = 227, 20.7%); and others (n = 204, 18.6%) (Fig. 1). Patient characteristics and epidemiology are shown in Table 1.

We first evaluated age as a confounding factor. The mean age of the 1097 patients was 58.7 (±17.5) years. The mean age of patients in the alcohol group was significantly lower than that of patients in the other 3 groups ($p < 0.0001$) (Table 1, S-Table 2). The alcohol group had a higher proportion of males than the other groups (>85% vs. <60%; $p < 0.0001$) (Table 1, S-Table 2). In line with Japanese Ministry of Health, Labor, and Welfare Severity Rating Scores, other differences in patient characteristics were found to be associated with these etiologies [10], i.e., lactate dehydrogenase levels were higher in the cholelithiasis group and platelet counts were lower in the alcohol group ($p < 0.05$) (Table 1, S-Table 2). Patients in the alcohol group received more EN within 48 h and were infused

**Table 1**
Patient characteristics and etiology.

| | Total (n = 1097) | Alcohol (n = 436) | Cholelithiasis (n = 230) | Idiopathic (n = 227) | Others (n = 204) | p-value |
|---|---|---|---|---|---|---|
| Characteristics | | | | | | |
| Age, mean (SD), y | 58.7 (17.5) | 50.0 (13.6) | 68.8 (15.0) | 63.0 (18.5) | 61.2 (17.9) | <0.0001 |
| Male gender, n (%) | 740 (67.5) | 382 (87.6) | 111 (48.3) | 127 (56.0) | 120 (58.8) | <0.0001 |
| APACHE II, mean (SD) | 12.8 (7.6) | 11.8 (7.8) | 13.2 (6.9) | 13.8 (7.7) | 13.3 (7.7) | 0.007 |
| Charlson index, median (interquartile) | 0 (0–1) | 0 (0–1) | 0 (0–1) | 0 (0–1) | 1 (0–2) | <0.0001 |
| Prognostic factor score, mean (SD) | 3.0 (2.3) | 2.9 (2.3) | 3.1 (2.0) | 3.3 (2.4) | 3.1 (2.3) | 0.10 |
| No. of patients with the following prognostic factor criteria* | | | | | | |
| Age ≥70 years | 358 (32.8) | 49 (11.2) | 124 (54.2) | 105 (46.9) | 80 (60.2) | <0.0001 |
| Number of positive measures in SIRS criteria ≥3 | 536 (49.2) | 217 (49.8) | 114 (49.8) | 108 (48.2) | 97 (48.3) | 0.97 |
| Base Excess ≤3 mEq/L or shock (systolic blood pressure <80 mmHg) | 347 (31.9) | 143 (32.8) | 68 (29.7) | 73 (32.6) | 63 (31.5) | 0.86 |
| $PaO_2$ ≤60 mmHg (room air) or respiratory failure (respirator management is needed) | 298 (27.4) | 108 (24.8) | 61 (26.6) | 67 (29.9) | 62 (31.0) | 0.31 |
| BUN ≥40 mg/dL (or Cr ≥ 2.0 mg/dL) or oliguria (daily urine output <400 mL even after IV fluid resuscitation) | 228 (20.9) | 91 (20.9) | 39 (17.0) | 60 (26.8) | 38 (18.9) | 0.06 |
| LDH ≥2 times of upper limit of normal | 438 (40.2) | 167 (38.3) | 122 (53.5) | 86 (38.4) | 63 (31.3) | <0.0001 |
| Platelet count ≤100,000/$mm^3$ | 174 (16.0) | 93 (21.3) | 27 (11.8) | 30 (13.4) | 24 (11.9) | 0.001 |
| Serum Ca ≤7.5 mg/dL | 359 (33.0) | 158 (36.2) | 54 (23.6) | 79 (35.4) | 68 (34.2) | 0.008 |
| CRP ≥15 mg/dL | 575 (52.8) | 225 (51.6) | 95 (41.5) | 137 (61.2) | 118 (58.7) | <0.0001 |
| CTSI (grading of pancreatitis, median (interquartile) | 4 (4–4) | 4 (4–4) | 4 (4–4) | 4 (4–4) | 4 (4–4) | 0.12 |
| CTSI (pancreatic necrosis), median (interquartile) | 0 (0–2) | 0 (0–2) | 0 (0–2) | 0 (0–4) | 0 (0–2) | <0.0001 |
| CTSI (total), median (interquartile) | | 4 (4–6) | 4 (4–6) | 4 (4–7) | 4 (4–6) | 0.004 |
| Revised Atlanta classification, n (%) | | | | | | 0.03 |
| Mild acute pancreatitis | 312 (28.4) | 132 (30.3) | 69 (30.0) | 60 (26.4) | 51 (25.0) | |
| Moderately SAP | 417 (38.0) | 171 (39.2) | 93 (40.4) | 70 (30.8) | 83 (40.7) | |
| SAP | 368 (33.6) | 133 (30.5) | 68 (29.6) | 97 (42.7) | 70 (34.3) | |
| Treatment | | | | | | |
| Enteral feeding within first 48 h, n (%) | 299 (27.3) | 138 (31.7) | 55 (23.9) | 63 (27.8) | 43 (21.1) | 0.02 |
| The amount of infused volume within first 24 h, mean (SD) | 5618 (3038) | 6137 (3231) | 4962 (2508) | 5555 (3132) | 5318 (2878) | <0.0001 |
| Dialysis due to renal failure, n (%) | 162 (14.8) | 60 (13.8) | 25 (10.9) | 43 (18.9) | 34 (16.7) | 0.08 |
| Use of ventilator, n (%) | 330 (30.1) | 118 (27.1) | 67 (29.1) | 89 (39.2) | 56 (27.5) | 0.009 |
| Preventive antibiotics, n (%) | 850 (77.5) | 318 (72.9) | 182 (79.1) | 180 (79.3) | 170 (83.3) | 0.02 |
| CRAI | 374 (34.1) | 166 (38.0) | 69 (30.0) | 82 (36.1) | 57 (27.9) | 0.04 |
| Protease inhibitor (intravenous) | 818 (74.6) | 307 (70.4) | 167 (72.6) | 174 (76.7) | 170 (83.3) | 0.004 |
| Outcomes | | | | | | |
| Mortality at hospital discharge, n (%) | 135 (12.3) | 36 (8.3) | 28 (12.2) | 38 (16.7) | 33 (16.2) | 0.004 |
| Mortality at 30 days, n (%) | 59 (5.4) | 16 (3.7) | 11 (4.8) | 18 (7.9) | 14 (6.9) | 0.09 |
| Mortality at 90 days, n (%) | 116 (10.6) | 35 (8.0) | 23 (10.0) | 31 (13.7) | 27 (13.2) | 0.08 |
| Pancreatic infection, n (%) | 136 (12.4) | 40 (9.2) | 38 (16.5) | 36 (15.9) | 22 (10.8) | 0.01 |
| Poly | 40 (3.7) | 13 (3.0) | 9 (4.0) | 9 (4.0) | 9 (4.4) | 0.13 |
| Mono | 83 (7.6) | 24 (5.5) | 24 (10.6) | 23 (10.3) | 12 (5.9) | |
| Surgical intervention, n (%) | 173 (15.8) | 50 (11.5) | 45 (19.6) | 48 (21.2) | 30 (14.7) | 0.003 |
| ICU days, median (interquartile) | 6 (0–12) | 6 (0–12) | 5 (1–12) | 7 (2–14) | 6 (0–12) | 0.20 |
| Hospital days, median (interquartile) | 24 (14–41) | 21 (13–35) | 25 (15–40) | 27 (16–58) | 28 (17–51) | <0.0001 |
| ICU admission | 811 (73.9) | 327 (75.0) | 175 (76.1) | 177 (78.0) | 132 (64.7) | 0.008 |

Values provided are patient numbers (percentage, statistically significant (SD), or interquartile range). The bold p-values indicate that there was a significant difference.
Abbreviations.
AKI: acute kidney injury, APACHE II: Acute Physiology and Chronic Health Evaluation, BUN: blood urea nitrogen, CRAI: continuous regional arterial infusion, CRP: C-reactive protein, CTSI: computed tomography severity index, ICU: intensive care unit, IV: intravenous, LDH: lactate dehydrogenase, MV: mechanical ventilation, $PaO_2$: partial pressure of oxygen in blood, SAP: severe acute pancreatitis, SD: standard deviation, SIRS: systemic inflammatory response syndrome.
*The number of total patients was 1089. Data was missing for eight patients.

with larger amounts of fluids than those in the others group ($p < 0.05$) (Table 1, S-Table 2). No difference was observed in the detection of microorganisms known to cause pancreatic infection among the four groups; the 2 most common microorganisms were methicillin-sensitive *Staphylococcus aureus* and *Enterococcus* (S-Table 3).

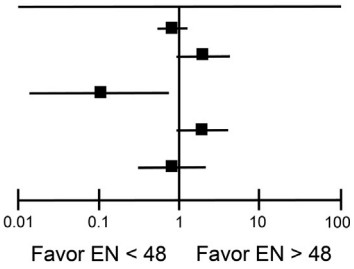
### *Association between SAP etiology and outcome*

We defined 2 major outcomes—in-hospital mortality (12.3% of total patients) and pancreatic infection (12.4% of total patients). Our post-hoc analysis demonstrated different likelihoods of possible outcomes for each etiology. Hospitalized patients with alcoholic SAP achieved better outcomes, namely significantly lower rates of in-hospital mortality and pancreatic infection, than those with idiopathic and other types of SAP ($p < 0.05$) (Table 1, S-Table 2). In all cases, mortality increased significantly with age ($p < 0.05$). Mortality also showed a general increase with age when analyzed for each etiology (S-Table 3).

We further analyzed the interaction between each confounding factor and the outcomes of in-hospital mortality and pancreatic infection (S-Table 5). According to interaction analysis results, EN within 48 h and use of prophylactic antibiotics may influence these results differently according to etiology. (S-Table 5). Subgroup analysis was conducted to analyze the interaction between the etiologies and these 2 factors (Fig. 2). Mortality was significantly decreased in the cholelithiasis group with early EN, but not for all SAP patients in general (Fig. 2a). The same effect was observed in patients in the others group given prophylactic antibiotics (Fig. 2b). Overall, it seems that confounding factors, such as type of

(A)

| Subject | EN < 48 (Death/Total) | EN > 48 (Death/Total) | Odds Ratio (95%CI) | P-value |
|---|---|---|---|---|
| Total | 31/299 | 104/798 | 0.77 (0.51 - 1.18) | 0.23 |
| Alcohol | 9/138 | 27/298 | 1.99 (0.92 - 4.33) | 0.37 |
| Cholelithiasis | 1/55 | 27/175 | 0.10 (0.01 - 0.77) | 0.03 |
| Idiopathic | 15/63 | 23/164 | 1.92 (0.92 - 3.97) | 0.08 |
| Others | 6/43 | 27/161 | 0.80 (0.31 - 2.09) | 0.66 |




(B)

| Subject | Pre-Abx+ (Death/Total) | Pre-Abx- (Death/Total) | Odds Ratio (95%CI) | P-value |
|---|---|---|---|---|
| Total | 104/850 | 31/247 | 0.97 (0.63-1.49) | 0.89 |
| Alcohol | 27/318 | 9/118 | 1.12 (0.51-2.47) | 0.77 |
| Cholelithiasis | 24/182 | 4/48 | 1.67 (0.55-5.07) | 0.37 |
| Idiopathic | 31/180 | 7/47 | 1.19 (0.49-2.90) | 0.70 |
| Others | 22/170 | 11/34 | 0.31 (0.13-0.73) | 0.007 |

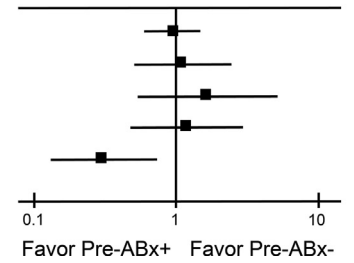



**Fig. 2.** Forest plots of in-hospital mortality; data are shown in the corresponding tables. (A) In-hospital mortality with or without enteral feeding (EN) within first 48 h. (B) In-hospital mortality with or without preventive antibiotics (Pre-Abx$^{-/+}$).

treatment, can lead to different outcomes in each etiological group.

*Multivariate and decision tree analyses of SAP etiology and outcome*

To determine how different confounding factors affect the outcomes in each etiological patient group, we performed univariable and multivariable analyses for in-hospital mortality and pancreatic infection. Increasing age and use of a ventilator had a significant, negative effect on in-hospital mortality regardless of etiology (Table 2). Early EN was significantly associated with reduced in-hospital mortality in the cholelithiasis and others group, while no significant association was observed in the alcohol and idiopathic group (Table 2). Prophylactic antibiotics reduced in-hospital mortality only in patients in the others groups (Table 2). With respect to pancreatic infection, age and early EN significantly increased the probability of pancreatic infection in the alcohol group, while CRAI and prophylactic antibiotics had no effect (Table 3).

To render our results into a simplified flow charts, we applied the decision tree method, which is based on the degree and order of factors that affect the outcomes. We generated decision tree models for all patients in each etiology, defining the ideal decision course for each physician who treated SAP patients (Figs. 3a and 4a). For example, mechanical ventilator use had a large influence on pancreatic infection. The Atlanta classification was the most influential factor on in-hospital mortality; the subsequent influential factors included RRT, APACHE II score, and age (Figs. 3a and 4a). Treatments performed after hospital admission did not significantly affect in-hospital mortality and were ranked lower in terms of clinical impact. Nevertheless, the form of the decision tree method differed for each etiology, and the types and order of factors affecting in-hospital mortality and pancreatic infection were also different (S-Table 6, Fig. 3b–e and 4b-e). S-Table 6 shows the order of branching factors in each etiology up to first 3 branches. In both outcomes, the impact on the outcomes and their order differed across the 4 etiological groups. The results were consistent with the results of the multivariate analysis. For example, in terms of in-hospital mortality, patients in the cholelithiasis and others groups, who also required ventilation, responded positively to treatment interventions, such as early EN and prophylactic antibiotics, respectively (Fig. 3c and e). In terms of pancreatic infection, patients in the alcohol group, who also required ventilation, responded positively to early EN (Fig. 4b). In summary, the results of our post-hoc analysis can be assembled to create a useful predictive tool.

## Discussion

The high morbidity and mortality in patients diagnosed with SAP demand better therapeutic approaches and improvement of present-day clinical practice [1,2,5,11]. Apart from the development of new therapies, epidemiological data can be useful for planning improved management strategies for SAP, depending on available treatments. We postulated that etiology should be considered when defining SAP prognosis and an appropriate acute treatment should be chosen. In this study, although the precise causal relationship between each etiology and patient background factors were unknown, it became clear that there is considerable heterogeneity among SAP patients. This wide heterogeneity would eventually be associated with clinical outcome, including risk of in-hospital mortality and pancreatic infection.

Across all etiologies, older age and mechanical ventilation use may negatively influence prognosis of SAP. However, the statistical associations between other confounding factors and clinical outcomes were dependent on patient etiology and background. To simplify our multivariate analyses, we generated decision tree models. A flow chart was constructed for each etiology and clinical outcome (e.g., in-hospital mortality and pancreatic infection) to show which confounding factors had the potential to improve or worsen prognosis. The calculated influence of severity scores on clinical outcome varied greatly in our study. Our decision tree models presented differences in the contributions of APACHE II score, Charlson index, revised Atlanta classification, and CTSI on in-hospital mortality or pancreatic infection, depending on etiology and patient background.

**Table 2**
Univariable and multivariable analysis: in-hospital mortality.

| | Total | | Alcohol | | Cholelithiasis | | Idiopathic | | Others | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| Age | | | | | | | | | | |
| Univariable | 1.04 (1.03–1.05) | <0.0001 | 1.06 (1.03–1.08) | <0.0001 | 1.04 (1.003–1.07) | 0.03 | 1.03 (1.007–1.06) | 0.011 | 1.03 (1.004–1.06) | 0.022 |
| Multivariable | 1.05 (1.03–1.06) | <0.0001 | 1.08 (1.04–1.12) | <0.0001 | 1.09 (1.04–1.16) | 0.0013 | 1.03 (0.99–1.07) | 0.06 | 1.02 (0.99–1.06) | 0.13 |
| Revised Atlanta Classification | | | | | | | | | | |
| Mild | | | | | | | | | | |
| Univariable | ref | | ref | | ref | | ref | | ref | |
| Multivariable | ref | | ref | | ref | | ref | | ref | |
| Moderate | | | | | | | | | | |
| Univariable | 1.29 (0.51–3.51) | 0.59 | 0.25 (0.01–2.00) | 0.20 | 1.90 (0.40–13.6) | 0.43 | $3.6*10^6$** | 0.052 | 0.92 (0.15–7.16) | 0.93 |
| Multivariable | 0.98 (0.38–2.74) | 0.97 | 0.20 (0.01–1.65) | 0.14 | 1.75 (0.29–14.2) | 0.55 | $8.6*10^7$** | 0.15 | 0.68 (0.10–5.84) | 0.70 |
| Severe | | | | | | | | | | |
| Univariable | 20.1 (9.87–48.2) | <0.0001 | 13.6 (4.70–57.8) | <0.0001 | 15.0 (4.12–96.4) | <0.0001 | $4.5*10^5$** | <0.0001 | 16.3 (4.54–104.9) | <0.0001 |
| Multivariable | 4.88 (2.07–13.0) | 0.0002 | 4.44 (1.06–23.7) | 0.04 | 4.76 (0.95–35.6) | 0.06 | $3.1*10^8$** | 0.01 | 2.96 (0.53–23.2) | 0.22 |
| Dialysis due to renal failure | | | | | | | | | | |
| Univariable | 11.1 (7.43–16.6) | <0.0001 | 15.0 (7.16–32.3) | <0.0001 | 8.69 (3.39–22.3) | <0.0001 | 13.0 (5.92–29.5) | <0.0001 | 8.00 (3.47–18.8) | <0.0001 |
| Multivariable | 3.86 (2.38–6.30) | <0.0001 | 5.52 (2.15–15.1) | <0.0001 | 6.32 (1.68–26.6) | 0.006 | 4.92 (1.96–13.0) | 0.0006 | 1.95 (0.66–5.71) | 0.23 |
| Use of ventilator | | | | | | | | | | |
| Univariable | 14.8 (9.37–23.5) | <0.0001 | 10.2 (4.62–22.4) | <0.0001 | 10.2 (4.07–25.4) | <0.0001 | 29.2 (8.61–98.9) | <0.0001 | 22.0 (8.35–58.2) | <0.0001 |
| Multivariable | 4.58 (2.47–8.73) | <0.0001 | 2.45 (0.78–8.15) | 0.13 | 5.73 (1.51–24.3) | 0.01 | 5.47 (1.21–33.2) | 0.03 | 10.6 (3.03–42.6) | 0.0001 |
| Enteral feeding within first 48 h | | | | | | | | | | |
| Univariable | 0.77 (0.51–1.18) | 0.23 | 0.70 (0.32–1.53) | 0.37 | 0.10 (0.01–0.77) | 0.027 | 1.92 (0.93–3.97) | 0.08 | 0.81 (0.31–2.10) | 0.66 |
| Multivariable | 0.47 (0.27–0.77) | 0.004 | 0.56 (0.21–1.39) | 0.22 | 0.03 (0.001–0.19) | <0.0001 | 1.08 (0.41–2.82) | 0.88 | 0.26 (0.07–0.86) | 0.03 |
| CRAI | | | | | | | | | | |
| Univariable | 2.03 (1.41–2.92) | 0.0001 | 1.73 (0.86–3.38) | 0.13 | 4.46 (1.96–10.1) | 0.0004 | 1.55 (0.76–3.13) | 0.23 | 2.19 (1.01–4.75) | 0.046 |
| Multivariable | 0.92 (0.56–1.50) | 0.74 | 0.58 (0.21–1.55) | 0.28 | 2.86 (0.88–9.46) | 0.08 | 0.59 (0.22–1.50) | 0.27 | 0.87 (0.28–2.61) | 0.81 |
| Preventive antibiotics | | | | | | | | | | |
| Univariable | 0.97 (0.63–1.49) | 0.89 | 1.12 (0.51–2.47) | 0.77 | 1.67 (0.55–5.07) | 0.37 | 1.19 (0.49–2.90) | 0.70 | 0.31 (0.13–0.73) | 0.007 |
| Multivariable | 0.92 (0.52–1.64) | 0.78 | 1.06 (0.38–3.13) | 0.91 | 1.86 (0.40–10.9) | 0.44 | 1.49 (0.46–5.21) | 0.51 | 0.26 (0.07–0.94) | 0.04 |
| Etiology | | | | | | | | | | |
| Alcohol | | | | | | | | | | |
| Cholelithiasis | | | | | | | | | | |
| Univariable | 1.54 (0.91–2.60) | 0.69 | | | | | | | | |
| Multivariable | 0.94 (0.47–1.87) | 0.86 | | | | | | | | |
| Idiopathic | | | | | | | | | | |
| Univariable | 2.23 (1.37–3.64) | 0.052 | | | | | | | | |
| Multivariable | 0.97 (0.51–1.84) | 0.92 | | | | | | | | |
| Others | | | | | | | | | | |
| Univariable | 2.14 (1.29–3.55) | 0.11 | | | | | | | | |
| Multivariable | 1.46 (0.74–2.84) | 0.27 | | | | | | | | |

Values given are odds ratios (confidence intervals). The bold p-values indicate that there was a significant difference.
Abbreviations: CI: confidence intervals, CRAI: continuous regional arterial infusion, OR: odds ratio.
**: Results were unstable because the number of in-hospital deaths was zero in idiopathic alcohol group, and that is why 95% CIs were not shown.

The association between age and mortality risk in SAP is well described in the literature [7,21,22], and our study confirmed this association across all etiologies. We found that younger patients were more likely to present with alcoholic pancreatitis, while older patients developed cholelithiasis-dependent and idiopathic pancreatitis. Although the association between increasing age and increasing mortality was observed in all etiologies, no significant difference was observed between the etiologies and in-hospital mortality. This may suggest that the lower mortality rate of patients with alcoholic pancreatitis was due to the high proportion of younger patients with alcoholic pancreatitis. As these results were obtained after adjusting for several confounding factors, there may be other factors contributing to the better prognosis in alcoholic patients or to the worse prognosis in other etiologies. Although mechanical ventilation might negatively influence SAP prognosis, we doubt that mechanical ventilation itself worsened prognosis; rather, its use indicated the severity of the case. A prospective study is necessary to show a causal association between these factors and mortality.

One of the major goals of this retrospective post-hoc analysis was to tailor, if possible, an ideal treatment plan for each etiological group. The choice of treatment by the attending physician varied

**Table 3**
Univariable and multivariable analyses: pancreatic infection.

| | Total | | Alcohol | | Cholelithiasis | | Idiopathic | | Others | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| Age | | | | | | | | | | |
| Univariable | 1.02 (1.01–1.03) | 0.003 | 1.03 (1.01–1.06) | 0.01 | 0.99 (0.97–1.01) | 0.32 | 1.02 (0.99–1.04) | 0.12 | 1.01 (0.98–1.03) | 0.66 |
| Multivariable | 1.05 (1.03–1.06) | <0.0001 | 1.03 (1.01–1.06) | 0.002 | 0.98 (0.96–1.01) | 0.23 | 1.01 (0.99–1.04) | 0.41 | 1.00 (0.97–1.03) | 0.80 |
| Revised Atlanta Classification | | | | | | | | | | |
| Mild | | | | | | | | | | |
| Univariable | ref | | ref | | ref | | ref | | ref | |
| Multivariable | ref | | ref | | ref | | ref | | ref | |
| Moderate | | | | | | | | | | |
| Univariable | 2.01 (1.04–4.13) | 0.04 | 2.39 (0.70–10.9) | 0.17 | 3.90 (1.21–17.4) | 0.02 | 1.76 (0.33–13.0) | 0.51 | 0.60 (0.14–2.62) | 0.48 |
| Multivariable | 0.98 (0.38–2.74) | 0.97 | 2.23 (0.63–10.4) | 0.22 | 2.86 (0.83–13.3) | 0.10 | 1.02 (0.16–8.15)) | 0.98 | 0.48 (0.10–2.20) | 0.33 |
| Severe | | | | | | | | | | |
| Univariable | 8.46 (4.71–16.6) | <0.0001 | 11.5 (3.92 (48.9) | <0.0001 | 9.83 (3.16–43.3) | <0.0001 | 13.0 (3.70–82.4) | <0.0001 | 2.94 (0.98–10.9) | 0.06 |
| Multivariable | 4.88 (2.07–13.0) | 0.0002 | 3.95 (1.06–19.4) | 0.04 | 3.54 (0.89–18.0) | 0.07 | 1.74 (0.25–15.2) | 0.58 | 0.84 (0.16–4.52) | 0.84 |
| Dialysis due to renal failure | | | | | | | | | | |
| Univariable | 4.41 (2.94–6.56) | <0.0001 | 4.68 (2.26–9.47) | <0.0001 | 2.75 (1.04–6.78) | 0.04 | 7.78 (3.58–17.2) | <0.0001 | 3.43 (1.26–8.86) | 0.02 |
| Multivariable | 3.86 (2.38–6.30) | <0.0001 | 1.23 (0.51–2.93) | 0.65 | 0.83 (0.28–2.33) | 0.72 | 2.79 (1.17–6.78) | 0.02 | 1.95 (0.60–6.16) | 0.26 |
| Use of ventilator | | | | | | | | | | |
| Univariable | 7.77 (5.25–11.7) | <0.0001 | 6.96 (3.51–14.5) | <0.0001 | 6.87 (3.29–15.0) | <0.0001 | 14.2 (5.70–43.3) | <0.0001 | 5.83 (2.34–15.5) | 0.0002 |
| Multivariable | 4.58 (2.47–8.73) | <0.0001 | 3.78 (1.45–10.1) | 0.006 | 3.98 (1.45–11.6) | 0.007 | 5.85 (1.45–28.6) | 0.01 | 3.84 (1.04–15.6) | 0.044 |
| Enteral feeding within first 48 h | | | | | | | | | | |
| Univariable | 1.00 (0.66–1.48) | 0.99 | 0.43 (0.17–0.94) | 0.03 | 1.60 (0.73–3.38) | 0.24 | 1.59 (0.74–3.35) | 0.23 | 1.12 (0.35–3.03) | 0.84 |
| Multivariable | 0.48 (0.28–0.79) | 0.004 | 0.33 (0.13–0.77) | 0.009 | 1.31 (0.54–3.05) | 0.54 | 1.00 (0.40–2.44) | 0.99 | 0.80 (0.22–2.48) | 0.71 |
| CRAI | | | | | | | | | | |
| Univariable | 2.37 (1.65–3.42) | <0.0001 | 2.39 (1.24–4.69) | 0.009 | 2.84 (1.39–5.83) | 0.004 | 2.27 (1.11–4.71) | 0.03 | 2.39 (0.95–5.91) | 0.63 |
| Multivariable | 0.92 (0.56–1.50) | 0.74 | 1.34 (0.61–3.00) | 0.45 | 1.78 (0.76–4.14) | 0.19 | 1.18 (0.49–2.80) | 0.71 | 2.18 (0.75–6.24) | 0.15 |
| Preventive antibiotics | | | | | | | | | | |
| Univariable | 1.08 (0.71–1.70) | 0.72 | 0.98 (0.48–2.11) | 0.77 | 1.49 (0.62–4.17) | 0.39 | 0.90 (0.39–2.25) | 0.81 | 0.89 (0.31–3.24) | 0.84 |
| Multivariable | 0.92 (0.52–1.64) | 0.78 | 1.10 (0.48–2.68) | 0.62 | 1.34 (0.48–4.22) | 0.59 | 1.11 (0.39–3.38) | 0.85 | 1.87 (0.51–8.59) | 0.36 |
| Etiology | | | | | | | | | | |
| Alcohol | ref | | | | | | | | | |
| Cholelithiasis | | | | | | | | | | |
| Univariable | 1.96 (1.22–3.16) | 0.006 | | | | | | | | |
| Multivariable | 0.94 (0.47–1.87) | 0.86 | | | | | | | | |
| Idiopathic | | | | | | | | | | |
| Univariable | 1.87 (1.15–3.02) | 0.01 | | | | | | | | |
| Multivariable | 0.97 (0.51–1.84) | 0.92 | | | | | | | | |
| Others | | | | | | | | | | |
| Univariable | 1.20 (0.68–2.05) | 0.53 | | | | | | | | |
| Multivariable | 1.46 (0.74–2.84) | 0.27 | | | | | | | | |

Values given are odds ratios (confidence intervals). The bold p-values indicate that there was a significant difference.
Abbreviations: CI: confidence intervals, CRAI: continuous regional arterial infusion, OR: odds ratio.

among etiological groups, but it did not necessarily align with our results, favoring one treatment over another. For example, although EN within 48 h was significantly associated with low mortality in overall multivariable analysis including all etiologies, the results of subgroup analysis showed that EN within 48 h was associated with low mortality only in patients with cholelithiasis. This suggests that overall mortality may be strongly influenced in patients with cholelithiasis. Thus, etiology may be one of the unknown reasons for controversy over the effectiveness of early EN [23–25]. Long-term fasting management has a poor prognosis because of atrophy of the intestinal mucosa, which may also relatively emphasize the effect of EN in gallstone pancreatitis [26]. One possible explanation is that in the case of gallstone pancreatitis, which is occasionally complicated with cholangitis, the fasting period may become longer than that in the other three etiologies due to initial treatment for cholangitis [27], thus leading to poor outcome. Similarly, prophylactic antibiotics were not effective in three etiologies (alcohol, gallstones, and idiopathic), which included approximately 80% patients in this cohort, whereas it was associated with low mortality for patients classified as “others.” Thus, the debate over the necessity for prophylactic antibiotics can be resolved by considering etiology with other possible confounding factors.

Although the order of the effect of the prognostic factors on the outcomes cannot be evaluated from the results of the simple multivariable analysis, the decision tree model may have the

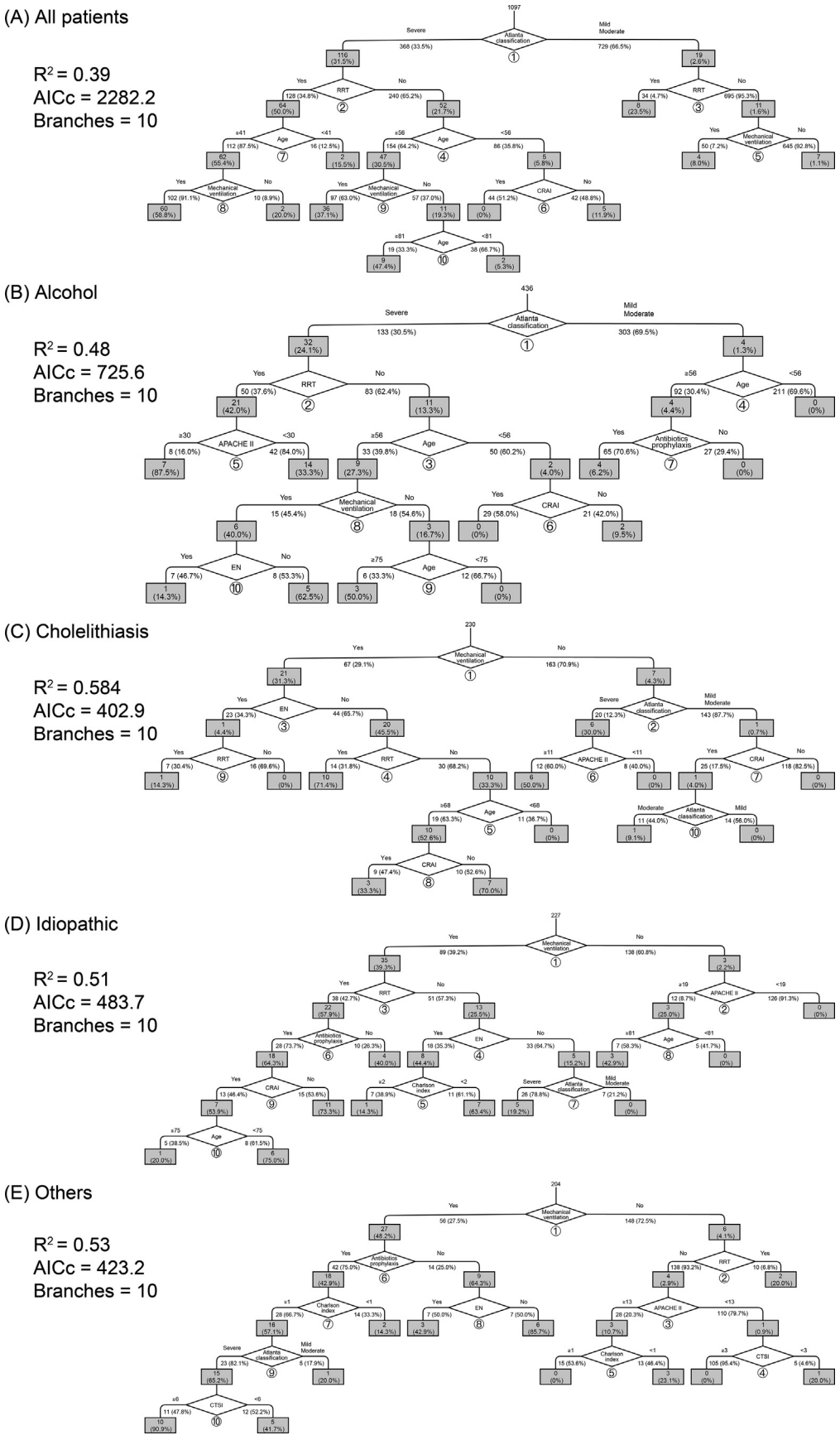



**Fig. 3.** Decision tree models—in-hospital mortality of patients according to patient etiology. (A) All patients. (B) Alcohol. (C) Cholelithiasis. (D) Idiopathic. (E) Others. Green diamonds indicate patient characteristics; blue diamonds indicate chosen treatments. Decision criteria per factor are shown above each branch, whereas patient numbers and percentages are shown below each branch. Gray rectangles show in-hospital mortality rates. The order of branching is shown below each diamond. Each branch is statistically significant as compared to the parallel branch ($p < 0.05$).

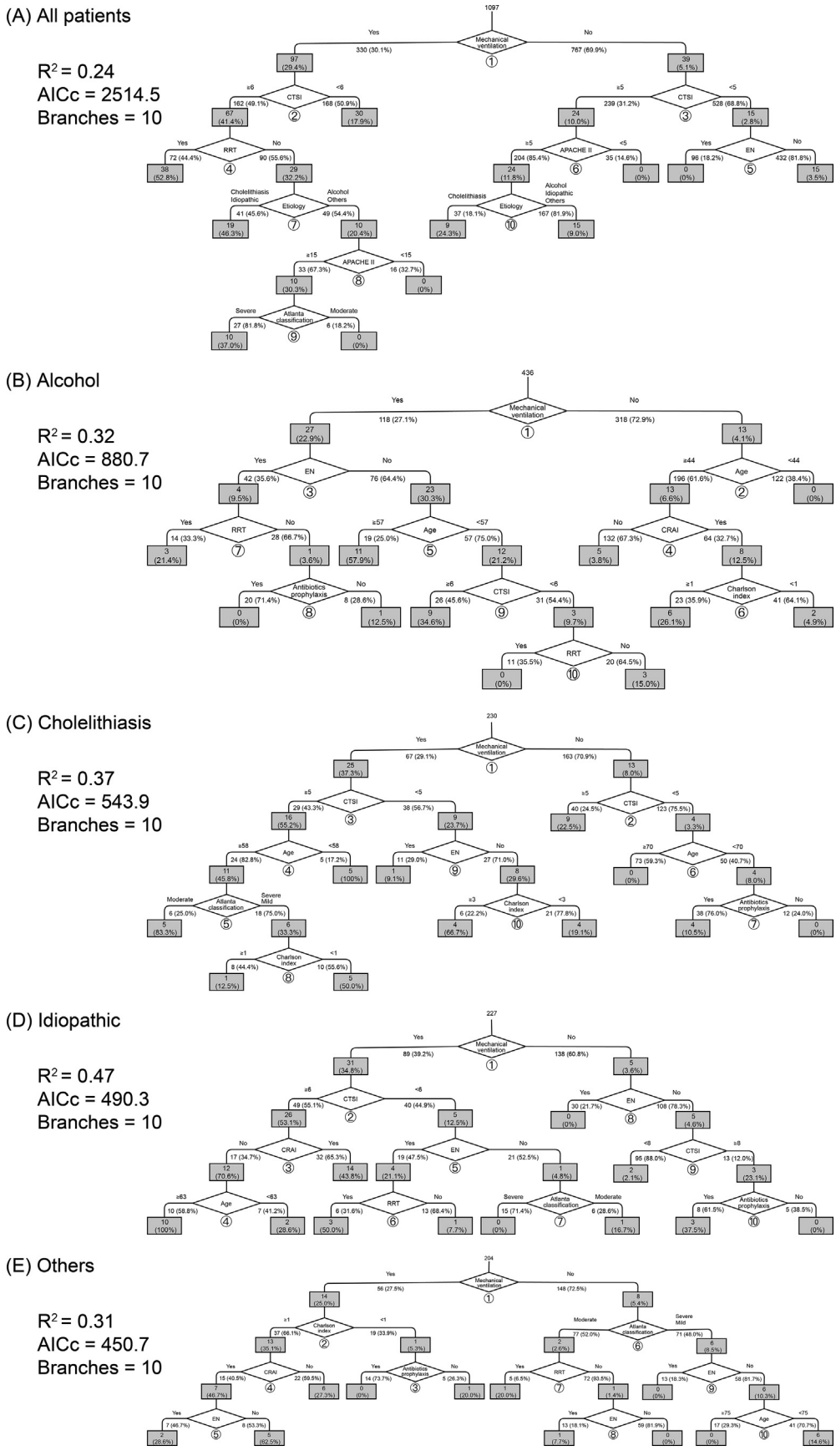



**Fig. 4.** Decision tree models—pancreatic infection in patients according to patient etiology. (A) All patients. (B) Alcohol. (C) Cholelithiasis. (D) Idiopathic. (E) Others. Green diamonds indicate patient characteristics; blue diamonds indicate chosen treatments. Decision criteria per factor are shown above each branch, whereas patient numbers and percentages are shown below each branch. Gray rectangles show pancreatic infection rates. The order of branching is shown below each diamond. Each branch is statistically significant as compared to the parallel branch ($p < 0.05$).

potential to evaluate this item. The decision tree model may suggest that certain patients with certain characteristics have a certain prognosis. For example, a patient with Atlanta Classification severe, RRT, age ≥44, and use of mechanical ventilation in Fig. 3 (a) may have the worst prognosis. The model may also help clinicians judge what characteristic affect prognosis the most (revised Atlanta Classification severe may be the most significant factor of patients presented in Fig. 3 (a)) and what the best value is to differentiate for dichotomous risk assessments. Most clinicians may be familiar with a similar dynamic risk assessment in the real world, which cannot be obtained by a comparison among mathematically calculated odds ratios from multivariable analysis for a whole population and may help in clinical decision making. Several previous studies have constructed prediction models using the methods of decision tree model [21,28–30], but these studies did not present the results of multivariable analysis, which is in contrast with our study.

In addition to the previously published models, we considered the included factors and their presenting sequence in the diagrams derived from the decision tree model differed across the 4 etiologies. The current study using a decision tree model along with a multivariable analysis may have the potential to develop a more systematic and practical approach for the management of each etiology of SAP. In the decision tree model, however, prognostic factors potentially with a large influence on the outcome sit at the top of diagram, and the impact of next prognostic factors on outcome can be evaluated for each subgroup after branching. This means that the impact of the factors on the outcome of patients not included in the subgroup cannot be evaluated. The decision tree model may be easier to apply to clinical judgements than the ordinary multivariable analysis, and this study, which analyzed the risk factors for several outcomes in each etiology, could present unique results that have not been shown in previous studies.

This study has several limitations. First, due to the relatively small sample size in each etiology after all SAP patients were divided into the 4 etiological groups, multivariate analysis including a sufficient number of confounding factors could not be performed. Although only 7 confounding factors were used, it is likely that more confounding factors exist. Second, more data are needed to assess the effectiveness of pancreatic necrosectomy, incidence of long-term complications, and out-of-hospital mortality, which were not monitored in this study. Finally, since our study was conducted exclusively in Japan, ethnicity may play an epidemiological role. There are no comparative data for the Japanese population, although mortality rates in this population seem to be lower [4]. Further clinical studies are required to validate our conclusions and prove causality.

In conclusion, our results and decision tree models demonstrate an added value in determining which clinical intervention is favored in specific patient groups. The study results can be used as a reference for improving clinical decisions and outcomes, including in-hospital mortality and pancreatic infection, depending on patient etiology and demographics. Further studies are warranted to test our decision tree model in prospective investigations.

## Funding

This study did not receive any funding.

## Declaration of competing interest

The authors declare no conflict of interest.

## Acknowledgments

We would like to acknowledge Kazuichi Okazaki, Tsuyoshi Hamada, Jun Kataoka, Tomohiro Adachi, Wataru Shinomiya, Shin Namiki, Kaoru Hirose, Sakue Masuda, Tomoaki Hashida, Naoki Shinyama, Hitoshi Yamamura, Takashi Moriya, Kunihiro Shirai,Kazuo Inui, Satoshi Yamamoto, Kyoji Oe, Takashi Muraki, Tetsuya Ito, Yukiko Masuda, Natsuko Tokuhira, Junichi Sakagami, Hiroaki Yasuda, Yoshinori Azumi, Masayuki Kamochi, Keiji Nagata, Nobuyuki Saito, Junko Izai, Kazunori Takeda, Motohiro Sekino, Tomoki Furuya, Yoshimoto Seki, Tetsuya Mine, Youhei Kawashima, Naoyuki Matsuda, Masato Inaba, Mineji Hayakawa, Takuyo Misumi and Yuki Takeda for their support with data collection at 44 institutions (Osaka Saiseikai Senri Hospital, Hiroshima City Hiroshima Citizens Hospital, Kansai Medical University Hirakata Hospital, The University of Tokyo Hospital, Iizuka Hospital, Japanese Red Cross Musashino Hospital, Tokyo Metropolitan Tama Medical Center, Japanese Red Cross Maebashi Hospital, Shonan Kamakura General Hospital, Showa University Hospital, Nihon University Hospital, Saiseikai Kumamoto Hospital, Fukuyama City Hospital, Jichi Medical University Hospital, Chiba University Hospital, Osaka City University Hospital, Tohoku University Hospital, Nihon University Itabashi Hospital, Gifu University Hospital, Fujita Health University Hospital, Asahi General Hospital, Shinshu University Hospital, National Hospital Organization Nagasaki Medical Center, University Hospital, Kyoto Prefectural University of Medicine, Mie University Hospital, Hospital of the University of Occupational and Environmental Health, Chiba-Hokusoh Hospital, Jichi Medical University, Saitama Medical Center, Wakayama Medical University Hospital, Tokyo Metropolitan Bokutoh Hospital, Jikei University Hospital, Saka General Hospital, Natinal Hospital Organization Sendai Medical Center, Nagasaki University Hospital, Keio University Hospital, Japanese Red Cross Akita Hospital, Ibaraki Prefectural Central Hospital, Tokai University Hospital, Nagoya University Hospital, Hokkaido University Hospital, National Cancer Center, Akita City Hospital, Kobe University Hospital, and Tokyo Rosai Hospital).

We thank the Japanese Society of Education for Physicians and Trainees in Intensive Care and the Japanese Society of Intensive Care Medicine.

We also thank to Editage for proofreading this manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2020.03.001.

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