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ORIGINAL ARTICLE

Infected pancreatic necrosis: outcomes and clinical predictors of mortality. A post hoc analysis of the MANCTRA-1 international study

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Abstract
The identification of high-risk patients in the early stages of infected pancreatic necrosis (IPN) is critical, because it could help the clinicians to adopt more effective management strategies. We conducted a post hoc analysis of the MANCTRA-1 international study to assess the association between clinical risk factors and mortality among adult patients with IPN. Univariable and multivariable logistic regression models were used to identify prognostic factors of mortality. We identified 247 consecutive patients with IPN hospitalised between January 2019 and December 2020. History of uncontrolled arterial hypertension ($p=0.032$; 95% CI 1.135–15.882; aOR 4.245), qSOFA ($p=0.005$; 95% CI 1.359–5.879; aOR 2.828), renal failure ($p=0.022$; 95% CI 1.138–5.442; aOR 2.489), and haemodynamic failure ($p=0.018$; 95% CI 1.184–5.978; aOR 2.661), were identified as independent predictors of mortality in IPN patients. Cholangitis ($p=0.003$; 95% CI 1.598–9.930; aOR 3.983), abdominal compartment syndrome ($p=0.032$; 95% CI 1.090–6.967; aOR 2.735), and gastrointestinal/intra-abdominal bleeding ($p=0.009$; 95% CI 1.286–5.712; aOR 2.710) were independently associated with the risk of mortality. Upfront open surgical necrosectomy was strongly associated with the risk of mortality ($p<0.001$; 95% CI 1.912–7.442; aOR 3.772), whereas endoscopic drainage of pancreatic necrosis ($p=0.018$; 95% CI 0.138–0.834; aOR 0.339) and enteral nutrition (p = 0.003; 95% CI 0.143–0.716; aOR 0.320) were found as protective factors. Organ failure, acute cholangitis, and upfront open surgical necrosectomy were the most significant predictors of mortality. Our study confirmed that, even in a subgroup of particularly ill patients such as those with IPN, upfront open surgery should be avoided as much as possible. Study protocol registered in ClinicalTrials.Gov (I.D. Number NCT04747990).

Part of this study was presented during the 8th International Congress of the World Society of Emergency Surgery (Edinburgh, U.K., 7–10 September 2021) and the United European Gastroenterology week 2022 (Vienna, 8–11 October 2022).

The members of the MANCTRA-1 Collaborative Group are mentioned in the Acknowledgements.

Extended author information available on the last page of the article

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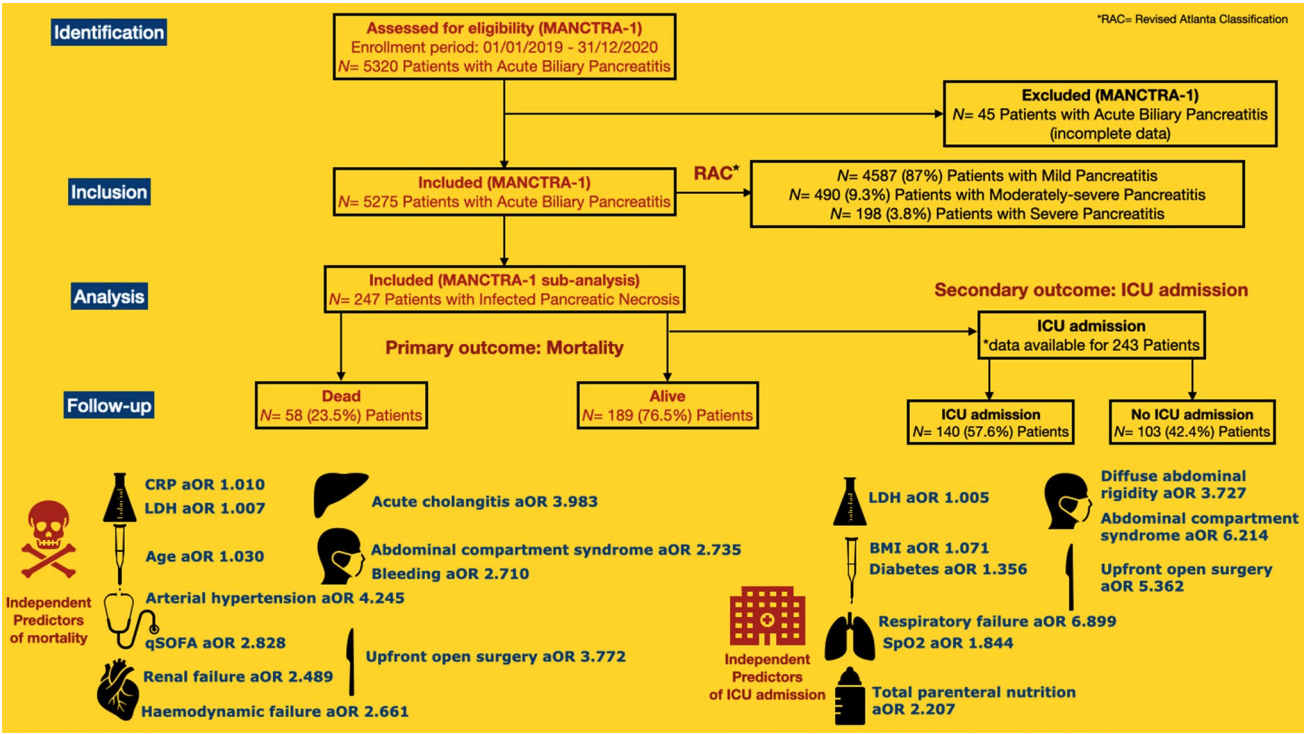
Graphical abstract



Keywords Acute pancreatitis · Infected pancreatic necrosis · International study · Organ failure · Mortality

Introduction

With an incidence of about 34 cases per 100,000 people, acute pancreatitis (AP) is the most frequent non-malignant gastroenterological disorder leading to hospitalisation worldwide [1–3]. Although 80% of AP patients have a mild self-limited clinical course, the other 20% will develop severe AP, characterised by pancreatic necrosis and organ failure, with a 35–50% mortality rate [4].

The early clinical course of severe AP is characterised by a dysregulated systemic inflammatory response syndrome, organ dysfunction, and acute fluid or necrotic collections. After recovery from the acute phase, 20% of patients present necrosis involving the pancreatic parenchyma, the surrounding fatty tissue, or both. While most necrotic collections remain sterile, about 30% of these patients will develop a superimposed necrosis infection, which is usually diagnosed by the presence of gas in the collections, positive culture of the pancreatic necrosis aspirate, and persistent sepsis or ongoing clinical deterioration. Prognostic factors associated with the development of infected pancreatic necrosis (IPN) in patients with acute necrotising or severe AP include older age, gallstone aetiology, greater than 50% necrosis of the pancreas, delayed enteral nutrition, multiple or persistent organ failure, and invasive mechanical ventilation [5]. Established scores such as the APACHE II and Ranson's have been proposed to grade disease severity and predict mortality. Similarly, several laboratory parameters, such as inflammatory markers, kidney function tests, and haematocrit have been trialled to accurately predict severe AP, development of necrosis and mortality [6]. Patients with IPN have been found to have higher APACHE II scores and higher values of lipase, C-reactive protein, and procalcitonin compared to patients with sterile necrosis [7].

With a mortality rate of up to 35%, IPN carries the clinical challenge of working with a multidisciplinary approach, determining proper timing for interventions, and identifying appropriate treatment strategies based on individual patient anatomy, pathophysiology, and local expertise [8–16]. Over the last decade, standard treatments of IPN have shifted from open surgical necrosectomy towards the so-called "step-up" endoscopic and percutaneous/minimally invasive approaches [17–22].

In the study by Wu et al. [23] aiming to investigate the risk factors for mortality among the population of patients with IPN, sequential organ failure assessment (SOFA) score > 2 and procalcitonin > 6 ng/L were independent predictors of mortality. Prognostic factors associated with the development of IPN in patients with acute necrotising or severe AP have been defined; on the other hand, although established scores such as the APACHE II and Ranson's have been used to predict mortality, the predictors of an increased mortality rate in those patients who develop IPN have not been described yet.

Study aim

Considering the high mortality rates associated with IPN, the identification of high-risk patients in the early stage of the disease (within 48–72 from hospital admission) is critical as it can help clinicians guide aggressive interventions and institute more effective management strategies to improve the prognosis. Thus, we conducted a post hoc analysis of the coMpliAnce with evideNce-based cliniCal guidelines in the managemenT of acute biliaRy pancreAtitis (MANCTRA-1) international study [24] to assess the association between clinical risk factors present early from hospital admission (within 72 h) and the subsequent development of fatal complications among adult patients with IPN, to implement potential mitigation strategies and improve survival outcomes.

Methods

Study design

The present study is a post hoc analysis of the MANCTRA-1 study, conducted in 150 centres in Europe, Asia, Africa, South America and Oceania [24, 25]. Ethical approval of the MANCTRA-1 study and subsequent post hoc analyses was granted by the Institutional Review Board of the University of Cagliari (Italy) (PROT. P.G./ 2021/5410–31/03/2021) and local boards of the participating centres. This study was conducted under the principles of the Declaration of Helsinki and was developed and presented according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE, ClinicalTrials. Gov NCT04747990) [26]. A retrospective analysis was performed on all consecutive patients hospitalised between January 2019 and December 2020 with a diagnosis of IPN associated with biliary pancreatitis. The exclusion criteria were the following: age younger than 16 years, patients with AP having an aetiology other than gallstones, history of chronic pancreatitis, pregnancy, or breastfeeding women.

Definitions

Necrotizing AP was defined as a lack of pancreatic parenchyma enhancement and/or findings of extra-pancreatic necrosis on contrast-enhanced computed tomography (CT) scan [14]. IPN was defined as contrast-enhanced CT scan evidence of gas collections in the pancreatic and/or extra-pancreatic tissues with evidence of sepsis identified with the increase of C-reactive protein (CRP) and procalcitonin, associated with fever and increased leukocytosis, abdominal pain, and deterioration of the clinical parameters and/or a positive culture of pancreatic necrosis obtained by fine-needle aspiration (FNA), percutaneous or endoscopic drainage or necrosectomy. Comorbidity was calculated on admission using the Charlson Comorbidity Index (CCI). The patients were classified as having severe AP based on persistent organ failure for more than 48 h, according to the revised Atlanta classification (RAC). Organ failure was defined as follows: respiratory failure (partial pressure of arterial oxygen-paO_2- < 60 mm), acute renal failure (serum creatinine > 2.0 mg/dL), haemodynamic failure (systolic blood pressure < 90 mmHg) any time during the first 72 h of hospital admission [14]. Obesity was defined according to the Centers for Disease Control (CDC) as patients with body mass index (BMI) > 30 kg/m^2. Abdominal compartment syndrome (ACS) was reported based on the World Society of the Abdominal Compartment Syndrome definition of sustained intra-abdominal pressure (IAP) > 20 mmHg associated with new organ dysfunction [27]. In-hospital mortality was defined as death occurring during hospitalisation for AP.

Outcomes

The study's primary endpoints were Intensive Care Unit (ICU) admission and in-hospital mortality. In addition, the following clinical outcomes were assessed, as defined above: organ failure (renal, respiratory, haemodynamic) during the hospital admission; the need for endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) and its timing; step-up endoscopic drainage of IPN; percutaneous drainage/minimally invasive necrosectomy; open surgical necrosectomy and its timing (early < 2 weeks from the onset of symptoms or late > 4 weeks); the setting of surgical necrosectomy (upfront, or after step-up approach attempts).

Variables of interest

For each patient, the following variables were analysed retrospectively to find possible associations between IPN and mortality risk or ICU admission.

1. Demographic data and baseline characteristics: sex, age, COVID-19 status on admission, previous episodes of

biliary AP, CCI, BMI, clinical history of diabetes, chronic pulmonary disease, arterial hypertension, atrial fibrillation, ischaemic heart disease, chronic kidney disease, diseases of the haematopoietic system, immunosuppressive medications;

2. Clinical risk scores calculated within 72 h from hospital admission: quick Sequential Organ Failure Assessment score (qSOFA), Bedside Index for Severity in Acute Pancreatitis (BISAP), Glasgow-Imrie, Ranson, Acute Physiology and Chronic Health Evaluation II (APACHE II);

3. Stage of the AP according to RAC, and systemic organ complications, including single or multiple organ failure within 72 h from hospital admission (haemodynamic, renal, respiratory);

4. Vital parameters: temperature, systolic blood pressure, heart rate, respiratory rate, and blood oxygen saturation;

5. Laboratory data: white blood cell (WBC) count, neutrophils, platelets, international normalised ratio (INR), CRP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, serum amylase, serum lipase, lactate dehydrogenase (LDH), procalcitonin, lactate;

6. Abdominal findings: diffuse abdominal pain, diffuse abdominal rigidity, localised abdominal pain, localised abdominal rigidity;

7. Concomitant findings: choledocholithiasis, acute cholangitis, timing and type of interventional procedures (ERCP/ES, endoscopic drainage of pancreatic necrosis, percutaneous drainage and minimally invasive necrosectomy, open surgical necrosectomy);

8. Occurrence of complications: ACS, bleeding, bowel fistula, and necrotising cholecystitis;

9. Type of supportive care: antibiotic therapy, antifungal therapy, and nutritional support.

Statistical analysis

Baseline characteristics of the study population were expressed as absolute numbers and relative frequency measurements for qualitative variables, whereas mean and standard deviation (SD) or the median and standard error (SE)/Interquartile Range (IQR) were used for the quantitative variables. The differences between groups for qualitative variables were determined using the X^2 test (with the Yates correction, when necessary) or Fisher's exact test as appropriate. Comparisons of quantitative variables between the two groups (survivors and non-survivors or patients admitted and non-admitted to ICU) were performed using the Student *t*-test for variables with parametric distribution and the Mann–Whitney *U* test for those with a non-parametric distribution. Univariable and multivariable logistic regression models were used to identify prognostic factors of mortality and ICU admission. Variables yielding *p* values < 0.05 by univariable analysis and clinical predictors for mortality and complications selected from relevant literature [5, 12, 28] were added to a stepwise prediction model according to their predictive value, indicated by pseudo R^2 (Negelkerke's R^2 and Cox & Snell R^2) until no further improvement of the model was achieved. The strength of association between a risk factor identified in univariable and multivariable analyses for mortality and ICU admission was determined by calculating odds ratios (OR) and adjusted odds ratios (aOR) with 95% confidence intervals (95% CI). Youden's J statistic was calculated to identify the optimal cut-point value of laboratory tests. To test model quality and its predictive performance, we plotted the receiver operating characteristics (ROC) curve and computed the area under the curve (AUROC) for the predictive models of mortality and ICU admission. A p value < 0.05 (two-tailed) was considered statistically significant. All the statistical analyses were performed using the Statistical Product and Service Solution (SPSS) 26.0 software (IBM SPSS Statistics, I.B.M. Corp., Armonk, NY, U.S.A.) and Jamovi Computer Software (The Jamovi project (2022). Jamovi (Version 2.3). Retrieved from https://www.jamovi.org).

Results

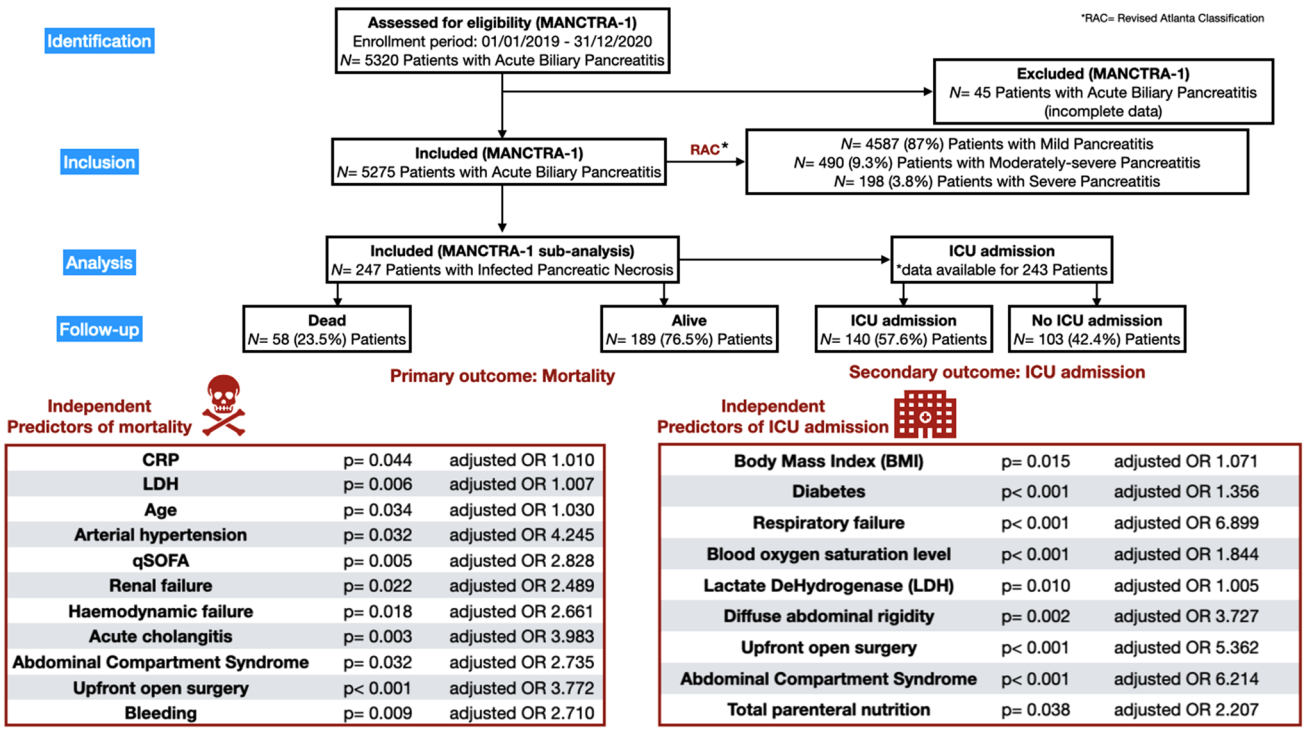
General characteristics of the cohort of patients

Over the two-year study period (January 2019–December 2020), a total of 5275 patients were included in the MANCTRA-1 database as they were admitted to any of the 150 participating general surgery, hepato-pancreato-biliary (HPB) surgery, gastroenterology or internal medicine departments for biliary AP; 4587 (87%) patients had mild AP, 490 (9.3%) patients had moderately severe AP, and 198 patients had severe AP (3.8%) according to the RAC determined within 72 h from the hospital admission [24]. Figure 1 is the study flowchart. Over the same study period, 247 patients who developed IPN during the hospital stay met the inclusion criteria and were considered for the final post hoc analysis on IPN (Table 1).

Predictors of ICU admission

The statistics for this outcome were performed on 243 patients (missed data for four patients, 1.6%).

The univariable analysis demonstrated a significant association between several demographic factors and the risk of ICU admission during the hospitalisation for IPN (Table 2). Mean BMI was higher in patients admitted to ICU than those who did not need ICU support ($p = 0.015$; MD 2.371). Similarly, diabetes was more common in



CRP	p= 0.044	adjusted OR 1.010
LDH	p= 0.006	adjusted OR 1.007
Age	p= 0.034	adjusted OR 1.030
Arterial hypertension	p= 0.032	adjusted OR 4.245
qSOFA	p= 0.005	adjusted OR 2.828
Renal failure	p= 0.022	adjusted OR 2.489
Haemodynamic failure	p= 0.018	adjusted OR 2.661
Acute cholangitis	p= 0.003	adjusted OR 3.983
Abdominal Compartment Syndrome	p= 0.032	adjusted OR 2.735
Upfront open surgery	p< 0.001	adjusted OR 3.772
Bleeding	p= 0.009	adjusted OR 2.710

Body Mass Index (BMI)	p= 0.015	adjusted OR 1.071
Diabetes	p< 0.001	adjusted OR 1.356
Respiratory failure	p< 0.001	adjusted OR 6.899
Blood oxygen saturation level	p< 0.001	adjusted OR 1.844
Lactate DeHydrogenase (LDH)	p= 0.010	adjusted OR 1.005
Diffuse abdominal rigidity	p= 0.002	adjusted OR 3.727
Upfront open surgery	p< 0.001	adjusted OR 5.362
Abdominal Compartment Syndrome	p< 0.001	adjusted OR 6.214
Total parenteral nutrition	p= 0.038	adjusted OR 2.207

Fig. 1 STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Flow-Diagram

patients admitted to ICU ($p < 0.001$; OR 1.321). Looking at the predictive scores, patients admitted to ICU had higher values of qSOFA ($p < 0.001$; MD 0.625), BISAP ($p = 0.021$; MD 0.644), Glasgow-Imrie ($p < 0.001$; MD 1.137), Ranson's ($p < 0.001$; MD 1.145), and APACHE II ($p = 0.035$; MD 2.247). A higher rate of patients with severe AP was found in patients admitted to ICU ($p < 0.001$; OR 7.137) and organ failure was more common in patients who needed ICU admission compared with those who did not ($p < 0.001$; OR 10.343). Respiratory failure showed the strongest association ($p < 0.001$; OR 10.765), followed by haemodynamic ($p < 0.001$; OR 3.713) and renal failure ($p < 0.001$; OR 3.187). Heart rate on admission was higher in patients admitted to ICU ($p = 0.008$; MD 6.374), whereas the mean blood oxygen saturation level was lower ($p < 0.001$; MD 2.001). On laboratory tests, patients admitted to ICU showed higher WBC count ($p = 0.003$; MD 1.874), CRP levels ($p = 0.049$; MD 34.423), LDH (p = 0.010; MD 252) and lactate ($p = 0.036$; MD 0.610).

Patients admitted to ICU more commonly had diffuse abdominal rigidity on hospital admission ($p = 0.002$; OR 1.235) and concomitant common bile duct obstruction ($p = 0.024$; OR 3.083). Patients with an indication for ERCP/ES (choledocholithiasis, common bile duct obstruction, cholangitis) were at increased risk of ICU admission if the procedure was performed later than 48 h ($p = 0.018$; OR 3.104) from hospital admission. Open surgical necrosectomy was associated with a higher risk of ICU admission ($p < 0.001$; OR 12.734).

Among the analysed complications of AP, ACS (p < 0.001; OR 11.534) was associated with the risk of ICU admission on the univariable analysis, followed by necrotising cholecystitis ($p = 0.005$; OR 6.524), bowel fistula ($p = 0.006$; OR 4.922), and bleeding ($p < 0.001$; OR 4.754). Total parenteral nutrition ($p = 0.038$; OR 1.793), but not enteral nutrition (p = 0.429; OR 0.803), was associated with a higher risk of ICU admission.

In the multivariable analysis, BMI ($p = 0.035$; aOR 1.071), diabetes (p = 0.018; aOR 1.356), severe AP ($p = 0.041$; aOR 4.464), respiratory failure ($p = 0.003$; aOR 6.899), blood oxygen saturation ($p < 0.001$; aOR 1.844), LDH ($p = 0.012$; aOR 1.005), diffuse abdominal rigidity ($p = 0.013$; aOR 3.727), upfront open surgical necrosectomy ($p = 0.028$; aOR 5.362), ERCP/ES performed > 48 h from hospital admission ($p = 0.026$, aOR 4.250), and total parenteral nutrition (p = 0.033; aOR 2.207) were independent predictors of ICU admission. Enteral feeding ($p = 0.040$; aOR 0.487) was shown to be a protective factor against the risk of ICU admission (Table 3).

The optimal cut-point was for BMI 34 kg/m^2 (Sensitivity 13.3%, Specificity 86.96%, PPV 40%, NPV 60.61%, Accuracy 60%), SpO_2 91% (Sensitivity 80.39%, Specificity 45.32%, PPV 51.9%, NPV 75.9%, Accuracy 61%), and

Table 1 General characteristics of the cohort of patients with infected pancreatic necrosis

Sample size (N. Patients)	247	Number (%)—Mean ± Standard Deviation and Median IQR
Sex (*N. %*)	Male	135 (54.7)
	Female	112 (45.3)
Age (Years)		59.2 ± 17.1; 61 IQR 25.0
COVID-19 Status on admission (*N. %*)	Negative	231 (93.5)
	Positive	16 (6.5)
Previous episodes of biliary pancreatitis (*N. %*)	Yes	83 (35.8)
	No	164 (64.2)
Admitting speciality (*N. %*)	HPB Surgery	43 (17.4)
	Gastroenterology	58 (23.5)
	General Surgery	116 (47.0)
	Internal Medicine	30 (12.1)
Setting of acquisition (*N. %*)	Community	219 (89.3)
	Hospital	28 (10.7)
Charlson's Comorbidity Index		2.94 ± 3.08; 2 IQR 3
Body Mass Index (BMI) Kg/m^2		27.5 ± 5.98; 27 IQR 8
Clinical history of diabetes (*N. %*)	Diabetes with organ disfunction	11 (4.5)
	Diabetes without organ disfunction	50 (20.2)
	No diabetes	186 (75.3)
Clinical history of chronic pulmonary disease (*N. %*)	Yes	36 (14.6)
	No	211 (85.4)
Clinical history of hypertension (*N. %*)	Yes	131 (53.0)
	No	116 (47.0)
Clinical history of atrial fibrillation (*N. %*)	Yes	29 (11.7)
	No	218 (88.3)
Clinical history of ischaemic heart disease (*N. %*)	Yes	27 (10.9)
	No	220 (89.1)
Clinical history of chronic kidney disease (*N. %*)	Yes—in permanent replacement therapy	1 (0.4)
	Yes—under medications	13 (5.3)
	No	233 (94.3)
Clinical history of diseases of the hematopoietic system (*N. %*)	Yes	6 (2.4)
	No	241 (97.6)
Patient on immunosuppressive medications (*N. %*)	Yes	10 (4.0)
	No	237 (96.0)
qSOFA		0.966 ± 1.03; 1 IQR 2.00
BISAP (Bedside Index of Severity in Acute Pancreatitis) score		2.10 ± 1.50; 2.00 IQR 2.00
Glasgow-Imrie criteria		2.85 ± 1.62; 3.00 IQR 2.00
Ranson's criteria		2.93 ± 1.62; 3.00 IQR 2.00
APACHE II score		8.06 ± 5.24; 7.00 IQR 5.00
Revised Atlanta Classification (RAC) stage (*N. %*)	Mild acute pancreatitis	88 (35.6)
	Moderately-severe acute pancreatitis	67 (27.1)
	Severe acute pancreatitis	92 (37.2)

Table 1 (continued)

Sample size (N. Patients)	247	Number (%)—Mean ± Standard Deviation and Median IQR
Organ failure during the hospital admission (*N. %*)	None	93 (37.7)
	Haemodynamic	26 (10.5)
	Haemodynamic—renal	5 (2.0)
	Haemodynamic—respiratory	9 (3.6)
	Haemodynamic—respiratory—renal	16 (6.5)
	Renal	41 (16.6)
	Respiratory	46 (18.6)
	Respiratory—renal	11 (4.5)
Temperature on admission °C		36.9 ± 1.36; 36.9 IQR 1.20
Systolic blood pressure on admission (mmHg)		125 ± 45.1; 120 IQR 34.00
Heart rate on admission (bpm)		92.1 ± 18.5; 90.0 IQR 26.00
Respiratory rate on admission (breaths/min)		19.0 ± 4.13; 18.0 IQR 6.00
Blood oxygen saturation level (SpO_2%) on admission		95.1 ± 3.81; 96.0 IQR 4.00
WBC on admission (cells/mm^3)		16.9 ± 6.5; 17.0 IQR 7.98
Neutrophils on admission (cells/mm^3)		14.1 ± 6.10; 14.1 IQR 7.90
Platelets on admission (mcL)		267 ± 129; 247 IQR 157
INR—International Normalised Ratio on admission		1.37 ± 0.654; 1.20 IQR 0.407
CRP—C-reactive Protein on admission (mg/L)		121 ± 125; 71.0 IQR 181
AST—Aspartate aminotransferase on admission (U/L)		180 ± 184; 104 IQR 217
ALT—Alanine aminotransferase on admission (U/L)		215 ± 286; 103 IQR 232
Total Bilirubin on admission (mg/dL)		2.65 ± 2.64; 1.60 IQR 2.41
Conjugated Bilirubin on admission (mg/dL)		1.54 ± 1.65; 0.910 IQR 1.60
Serum Amylase on admission (U/L)		1463 ± 1440; 901 IQR 1702
Serum Lipase on admission (U/L)		2870 ± 3540; 1270 IQR 3700
LDH—Lactate DeHydrogenase on admission (U/L)		531 ± 510; 410 IQR 314
Procalcitonin on admission (*N*g/mL)		3.78 ± 6.40; 1.66 IQR 3.60
Lactates on admission (mmol/L)		2.65 ± 1.54; 2.25 IQR 1.92
Abdominal findings (*N. %*)	Diffuse abdominal pain	99 (40.1)
	Diffuse abdominal rigidity	30 (12.1)
	Localised abdominal pain	91 (36.8)
	Localised abdominal rigidity	20 (8.1)
	No abdominal pain/no abdominal rigidity	7 (2.8)
Concomitant choledocholithiasis (*N. %*)	No	164 (66.4)
	Yes	59 (23.9)
	Yes, with common bile duct obstruction	24 (9.7)
Concomitant cholangitis (*N. %*)	Yes	36 (14.6)
	No	211 (85.4)
ERCP/ES (*N. %*)	No	187 (75.7)
	Yes, within 24 h from hospital admission	8 (3.2)
	Yes, between 24–48 h from hospital admission	18 (7.3)
	Yes, between 48–72 h from hospital admission	19 (7.7)
	Yes, > 72 h from hospital admission	15 (6.1)
Endoscopic step-up drainage of pancreatic necrosis (*N. %*)	Yes	56 (22.7)
	No	191 (77.3)

Table 1 (continued)

Sample size (N. Patients)	247	Number (%)—Mean ± Standard Deviation and Median IQR
Surgical necrosectomy (*N. %*)	No	162 (65.9)
	Yes, minimally-invasive	63 (25.6)
	Yes, open	22 (8.5)
Timing of surgical necrosectomy (*N. %*)	< 2 weeks from the onset of symptoms	27 (32.0)
	2–4 weeks from the onset of symptoms	28 (32.0)
	> 4 weeks from the onset of symptoms	30 (36.0)
Setting of surgical necrosectomy (*N. %*)	Upfront	54 (61.3)
	After failure of endoscopic necrosectomy attempt	8 (8.6)
	After failure of percutaneous and endoscopic necrosectomy attempt	23 (30.1)
Abdominal compartment syndrome (*N. %*)	Yes	28 (11.3)
	No	219 (88.7)
Bleeding (*N. %*)	Yes	44 (17.8)
	No	203 (82.2)
Bowel fistula (*N. %*)	Yes	21 (8.5)
	No	226 (91.5)
Necrotizing cholecystitis (*N. %*)	Yes	18 (7.3)
	No	229 (92.7)
Antibiotic therapy (*N. %*)	Yes	212 (85.8)
	No	35 (14.2)
Antifungal therapy (*N. %*)	Yes	91 (36.8)
	No	156 (63.2)
Nutritional support (*N. %*)	Nihil per os	63 (25.5)
	Total parenteral nutrition	85 (34.4)
	Oral	47 (19.0)
	Enteral via naso-gastric tube	31 (12.5)
	Enteral via naso-jejunal tube	21 (8.5)
ICU admission (*N. %*)	Yes	140 (57.6)
	No	103 (42.4)
Mortality (*N. %*)	Yes	58 (23.5%)
	No	189 (76.5%)

HPB Hepato-pancreato-biliary, *RAC* Revised Atlanta Classification, *qSOFA* quick Sepsis-related Organ Failure Assessment, *BISAP* Bedside Index of Severity in Acute Pancreatitis, *APACHE II* Acute Physiology, Age, and Chronic Health Evaluation II, *ERCP/ES* Endoscopic Retrograde Cholangio-Pancreatography/Endoscopic Sphincterotomy

LDH 554 U/L (Sensitivity 21.43%, Specificity 60.49%, PPV 23.6%, NPV 68.3%, Accuracy 65%).

ROC curves were plotted to assess the performance of the combination of the parameters above to predict ICU admission in patients with IPN. The final stepwise multivariable logistic regression model (logistic regression X^2 36.3; $p < 0.001$; pseudo R^2 0.309; Nagelkerke R^2 0.425; McFadden's R^2 0.284) consisted of 9 variables (Fig. 2). Calibration of the model determined quantitatively by the Hosmer–Lemeshow goodness of fit statistics (LH X^2 3.07, $p = 0.047$) confirmed that the model could assign appropriate risk among the patients whose experience is simulated by the model. As a result of discrimination evaluated using ROC analysis, the model's accuracy was 72.4%, specificity was 57.1%, and sensitivity was 81.0%, with an AUROC = 0.830.

Predictors of mortality

Overall mortality in the whole cohort of patients with IPN was 23.5%. Factors associated with mortality at univariable analysis are reported in Table 3. Mean age was higher in the non-survivor group than in survivors ($p = 0.05$; MD 5.001). Similarly, the mean CCI ($p = 0.021$; MD 1.003) and BMI ($p = 0.012$; MD 2.701) were higher in the non-survivor group compared to survivors.

Table 2 Results of the univariable and multivariable analyses. Outcome intensive care unit (ICU) admission

Predictor ICU admission (*N.* Patients, %)	Yes = 140 (57.6)	No = 103 (42.4)	Odds ratio (OR) or Mean difference (MD)	95% CI	*p*-value	adjusted OR (aOR)	95% CI	*p*-value
Sex (*N. %*)								
Female	65 (46.4)	45 (43.6)	OR = 0.895	[0.537; 1.492]	0.672			
Male	75 (53.6)	58 (56.4)						
Age (Years) Mean ± SD (Median; SE)	58.6 ± 15.4 (60.5; 1.4)	60.4 ± 19.2 (61.0; 1.89)	MD = 1.851	[– 2.53; 1.231]	0.407			
COVID-19 Status on admission (*N. %*)								
Negative	129 (92.1)	97 (94.2)	OR = 1.383	[0.493; 3.863]	0.539			
Positive	11 (7.9)	6 (5.8)						
Previous episodes of biliary pancreatitis (*N. %*)								
No	93 (66.4)	67 (65.0)	OR = 0.941	[0.550:1.612]	0.823			
Yes	47 (33.6)	36 (35.0)						
Admitting speciality (*N. %*)								
HPB Surgery	27 (19.3)	16 (15.5)	OR = 1.302	[0.659; 2.561]	0.449			
Other	113 (80.7)	87 (84.5)						
Charlson's Comorbidity Index Mean ± SD (Median; SE)	3.05 ± 3.98 (2.00; 0.337)	2.97 ± 2.60 (3.00; 0.256)	MD = 0.079	[– 0.965; 0.807]	0.649			
Body Mass Index (BMI) Kg/m^2 Mean ± SD (Median; SE)	28.2 ± 5.88 (27.1; 0.613)	25.9 ± 5.71 (25.7; 0.737)	MD = 2.371	[– 4.281; – 0.467]	0.015	1.071	[1.004; 1.143]	0.035
Clinical history of diabetes (*N. %*)								
No	94 (67.1)	89 (86.4)	OR = 1.321	[1.165; 1.625]	< 0.001	1.356	[1.150; 1.841]	0.018
Yes	46 (32.9)	14 (13.6)						
Clinical history of chronic pulmonary disease (*N. %*)								
No	115 (82.1)	92 (89.3)	OR = 1.823	[0.850; 3.892]	0.120			
Yes	25 (17.9)	11 (10.7)						
Clinical history of hypertension (*N. %*)								
No	66 (47.1)	49 (47.6)	OR = 1.021	[0.611; 1.694]	0.947			
Yes	74 (52.9)	54 (52.4)						
Clinical history of atrial fibrillation (*N. %*)								
No	121 (86.4)	93 (90.3)	OR = 1.463	[0.648; 3.291]	0.359			
Yes	19 (13.6)	10 (9.7)						

Table 2 (continued)

Predictor ICU admission (*N.* Patients, %)	Yes = 140 (57.6)	No = 103 (42.4)	Odds ratio (OR) or Mean difference (MD)	95% CI	*p*-value	adjusted OR (aOR)	95% CI	*p*-value
Clinical history of ischaemic heart disease (*N.* %)								
No	123 (87.8)	95 (92.2)	OR = 1.642	[0.679; 3.962]	0.267			
Yes	17 (12.2)	8 (7.8)						
Clinical history of chronic kidney disease (*N.* %)								
No	133 (95.0)	96 (93.2)	OR = 0.722	[0.245; 2.137]	0.533			
Yes	7 (5.0)	7 (6.8)						
Clinical history of diseases of the hematopoietic system (*N.* %)								
No	138 (98.6)	99 (96.1)	OR = 0.359	[0.064; 2.004]	0.223			
Yes	2 (1.4)	4 (3.9)						
Patient on immunosuppressive medications (*N.* %)								
No	135 (96.4)	98 (95.1)	OR = 0.726	[0.205; 2.587]	0.619			
Yes	5 (3.6)	5 (4.9)						
qSOFA Mean ± SD (Median; SE)	1.21 ± 1.03 (1.00; 0.106)	0.588 ± 0.920 (0.00; 0.129)	MD = 0.625	[– 0.965; – 0.284]	< 0.001	1.550	[0.762; 3.152]	0.226
BISAP score Mean ± SD (Median; SE)	2.35 ± 1.53 (2.00; 0.165)	1.70 ± 1.39 (2.00; 0.210)	MD = 0.644	[– 1.197; – 0.099]	0.021	0.760	[0.460; 1.254]	0.283
Glasgow-Imrie criteria Mean ± SD (Median; SE)	3.30 ± 1.52 (3.00; 0.169)	2.16 ± 1.53 (2.00; 0.233)	MD = 1.137	[– 1.703; – 0.565]	< 0.001	1.290	[0.722; 2.303]	0.389
Ranson's criteria Mean ± SD (Median; SE)	3.36 ± 1.56 (3.00; 0.167)	2.21 ± 1.46 (2.00; 0.225)	MD = 1.145	[– 1.715; – 0.575]	< 0.001	1.476	[0.875; 2.489]	0.144
APACHE II score Mean ± SD (Median; SE)	9.11 ± 5.95 (7.00; 0.756)	6.87 ± 3.37 (7.00; 0.540)	MD = 2.247	[– 4.323; – 0.165]	0.035	1.096	[0.953; 1.260]	0.198
Revised Atlanta Classification (RAC) stage (*N.* %)								
Moderately severe	45 (32.1)	22 (21.3)	OR = 1.745	[0.967; 3.153]	0.063			
Severe	74 (52.8)	14 (13.6)	OR = 7.137	[3.712; 13.735]	< 0.001	4.464	[1.061; 18.787]	0.041
Organ failure during the hospital admission (*N.* %)								
No	34 (24.3)	69 (66.9)	OR = 10.343	[5.631; 18.903]	< 0.001	0.835	[0.139; 5.020]	0.844
Yes	106 (75.7)	34 (33.1)						

Table 2 (continued)

Predictor ICU admission (*N.* Patients, %)	Yes = 140 (57.6)	No = 103 (42.4)	Odds ratio (OR) or Mean difference (MD)	95% CI	*p*-value	adjusted OR (aOR)	95% CI	*p*-value
Renal failure during the hospital admission (*N.* %)								
No	86 (61.4)	86 (83.5)	OR = 3.187	[1.712; 5.916]	< 0.001	2.380	[0.676; 8.383]	0.177
Yes	54 (38.6)	17 (16.5)						
Haemodynamic failure during the hospital admission (*N.* %)								
No	97 (69.3)	92 (89.3)	OR = 3.713	[1.801; 7.634]	< 0.001	2.267	[0.645; 7.972]	p = 0.202
Yes	43 (30.7)	11 (10.7)						
Respiratory failure during the hospital admission (N. %)								
No	69 (49.3)	94 (91.3)	OR = 10.765	[5.031; 23.076]	< 0.001	6.899	[1.951; 24.396]	0.003
Yes	71 (50.7)	9 (8.7)						
Temperature on admission °C Mean ± SD (Median; SE)	37.0 ± 1.66 (37.0; 0.141)	36.8 ± 0.812 (36.6; 0.0800)	MD = 0.196	[– 0.545; 0.154]	0.271			
Systolic blood pressure on admission (mmHg) Mean ± SD (Median; SE)	121 ± 56.6 (110; 4.78)	129 ± 22.0 (128; 2.17)	MD = 7.837	[– 3.764; 19.454]	0.184			
Heart rate on admission (bpm) Mean ± SD (Median; SE)	94.8 ± 18.3 (95.0; 1.55)	88.4 ± 18.7 (87.0; 1.84)	MD = 6.374	[– 11.143; – 1.614]	0.008	1.013	[0.997; 1.028]	0.113
Respiratory rate on admission (breaths/min) Mean ± SD (Median; SE)	19.8 ± 4.68 (19.0; 0.397)	18.7 ± 6.87 (18.0; 0.680)	MD = 1.087	[– 2.556; 0.385]	0.148			
Blood oxygen saturation level (SpO_2%) on admission Mean ± SD (Median; SE)	94.2 ± 4.45 (95.0; 0.378)	96.2 ± 2.36 (96.0; 0.234)	MD = 2.001	[1.053; 2.964]	< 0.001	1.844	[1.764; 1.931]	< 0.001
WBC on admission (cells/mm^3) Mean ± SD (Median; SE)	17.8 ± 6.35 (18.0; 0.548)	15.9 ± 6.62 (15.7; 0.676)	MD = 1.874	[– 3.576; – 0.168]	0.031	1.226	[0.861; 1.749]	0.258
Neutrophils on admission (cells/mm^3) Mean ± SD (Median; SE)	14.8 ± 6.41 (14.5; 0.590)	13.4 ± 5.67 (13.1; 0.588)	MD = 1.393	[– 3.063; 0.276]	0.101			

Table 2 (continued)

Predictor ICU admission (*N.* Patients, %)	Yes = 140 (57.6)	No = 103 (42.4)	Odds ratio (OR) or Mean difference (MD)	95% CI	*p*-value	adjusted OR (aOR)	95% CI	*p*-value
Platelets on admission (mcL) Mean ± SD (Median; SE)	268 ± 136 (252; 11.8)	265 ± 123 (237; 12.5)	MD = 3.704	[– 38.216; 30.810]	0.833			
INR—International Normalised Ratio on admission Mean ± SD (Median; SE)	1.39 ± 0.637 (1.20; 0.0582)	1.33 ± 0.693 (1.14; 0.0765)	MD = 0.677	[– 0.254; 0.119]	0.476			
CRP—C-reactive Protein on admission (mg/L) Mean ± SD (Median; SE)	130 ± 131 (85.7; 12.5)	95.9 ± 103 (49.0; 11.3)	MD = 34.423	[– 68.712; – 0.153]	0.049	1.006	[0.999; 1.014]	0.085
AST—Aspartate aminotransferase on admission (U/L) Mean ± SD (Median; SE)	189 ± 187 (116.0; 17.7)	168 ± 183 (84.0; 21.2)	MD = 21.134	[– 75.712; 33.532]	0.446			
ALT—Alanine aminotransferase on admission (U/L) Mean ± SD (Median; SE)	216 ± 280 (110; 25.1)	218 ± 299 (92.5; 30.5)	MD = 2.224	[– 74.923; 79.411]	0.955			
Total Bilirubin on admission (mg/dL) Mean ± SD (Median; SE)	2.93 ± 2.85 (2.00; 0.250)	2.30 ± 2.34 (1.46; 0.239)	MD = 0.636	[– 1.341; 0.064]	0.075			
Conjugated Bilirubin on admission (mg/dL) Mean ± SD (Median; SE)	1.60 ± 1.74 (0.900; 0.177)	1.46 ± 1.54 (0.920; 0.211)	MD = 0.140	[– 0.705; 0.424]	0.624			
GGT—Gamma-Glutamyl Transpeptidase on admission (U/L) Mean ± SD (Median; SE)	287 ± 301 (197; 32.8)	217 ± 236 (116; 32.1)	MD = 70.010	[– 166.621; 25.634]	0.150			
Serum Amylase on admission (U/L) Mean ± SD (Median; SE)	1490 ± 1531 (829; 149)	2621 ± 5196 (983; 596)	MD = 1131.103	[0.017; 0.616]	0.036	0.997	[0.993; 1.000]	0.056
Serum Lipase on admission (U/L) Mean ± SD (Median; SE)	3907 ± 6652 (1098; 701)	4920 ± 6714 (2105; 814)	MD = 1013.103	[– 1107–3133]	0.347			

Table 2 (continued)

Predictor ICU admission (*N.* Patients, %)	Yes = 140 (57.6)	No = 103 (42.4)	Odds ratio (OR) or Mean difference (MD)	95% CI	*p*-value	adjusted OR (aOR)	95% CI	*p*-value
LDH—Lactate DeHydrogenase on admission (U/L) Mean ± SD (Median; SE)	625 ± 606 (476; 67.4)	373 ± 183 (313; 28.2)	MD = 252.112	[– 441; – 61.7]	0.010	1.005	[1.001; 1.009]	0.012
Procalcitonin on admission (ng/mL) Mean ± SD (Median; SE)	4.50 ± 6.53 (2.95; 0.932)	2.38 ± 6.12 (0.400; 1.28)	MD = 2.131	[– 5.351; 1.102]	0.193			
Lactates on admission (mmol/L) Mean ± SD (Median; SE)	2.89 ± 1.60 (2.70; 0.193)	2.28 ± 1.37 (1.90; 0.200)	MD = 0.610	[– 1.183; – 0.041]	0.036	1.470	[0.877; 2.463]	0.143
Diffuse abdominal pain (*N.* %)								
No	85 (60.7)	62 (60.2)	OR = 1.023	[0.607; 1.724]	0.935			
Yes	55 (39.3)	41 (39.8)						
Diffuse abdominal rigidity (*N.* %)								
No	115 (82.1)	98 (95.1)	OR = 1.235	[1.086; 1.636]	0.002	3.727	[1.315; 10.560]	0.013
Yes	25 (17.9)	5 (4.9)						
Concomitant choledocholithiasis (*N.* %)								
No	90 (64.3)	72 (69.9)	OR = 1.291	[0.748; 2.223]	0.359			
Yes	50 (35.7)	31 (30.1)						
Concomitant common bile duct obstruction (*N.* %)								
No	121 (86.4)	98 (95.1)	OR = 3.083	[1.112; 8.541]	0.024	2.346	[0.733; 7.120]	0.132
Yes	19 (13.6)	5 (4.9)						
Concomitant acute cholangitis (*N.* %)								
No	114 (81.4)	93 (90.3)	OR = 2.124	[0.974; 4.621]	0.055	1.692	[0.717; 3.990]	0.230
Yes	26 (18.6)	10 (9.7)						
ERCP/ES > 48 h for concomitant choledocholithiasis, common bile duct obstruction, or cholangitis (*N.* %)								
No	29 (49.1)	27 (75.0)	OR = 3.104	[1.253; 7.721]	0.018	4.250	[1.190; 15.180]	0.026
Yes	30 (50.9)	9 (25.0)						

Table 2 (continued)

Predictor ICU admission (*N.* Patients, %)	Yes = 140 (57.6)	No = 103 (42.4)	Odds ratio (OR) or Mean difference (MD)	95% CI	*p*-value	adjusted OR (aOR)	95% CI	*p*-value
ERCP/ES ≤ 48 h for concomitant choledocholithiasis, common bile duct obstruction, or cholangitis (*N.* %)								
No	40 (67.8)	30 (83.3)	OR = 2.382	[0.846; 6.673]	0.149			
Yes	19 (32.2)	6 (16.7)						
Endoscopic step-up drainage of pancreatic necrosis (*N.* %)								
No	101 (72.1)	86 (83.5)	OR = 1.953	[1.031; 3.702]	0.045	1.755	[0.319; 9.670]	0.518
Yes	39 (27.9)	17 (16.5)						
Upfront open surgical necrosectomy (*N.* %)								
No	85 (60.7)	98 (95.1)	OR = 12.734	[4.852; 33.110]	< 0.001	5.362	[1.199; 23.990]	0.028
Yes	55 (39.3)	5 (4.9)						
Percutaneous drainage/minimally invasive necrosectomy (*N.* %)								
No	125 (89.3)	97 (94.2)	OR = 1.941	[0.726; 5.193]	0.248			
Yes	15 (10.7)	6 (5.8)						
Surgical necrosectomy < 2 weeks from the onset (*N.* %)								
No	49 (66.2)	16 (88.9)	OR = 4.001	[0.847; 18.902]	0.081			
Yes	25 (33.8)	2 (11.1)						
Surgical necrosectomy 2–4 weeks from the onset (*N.* %)								
No	22 (52.4)	11 (57.9)	OR = 2.853	[0.944; 8.601]	0.074			
Yes	20 (47.6)	8 (42.1)						
Surgical necrosectomy > 4 weeks from the onset (*N.* %)								
No	48 (66.7)	12 (66.6)	OR = 1.012	[0.331; 3.063]	0.990			
Yes	24 (33.3)	6 (33.4)						
Upfront surgical necrosectomy (*N.* %)								
No	29 (38.2)	7 (50.0)	OR = 1.591	[0.504; 4.992]	0.428			
Yes	47 (61.8)	7 (50.0)						

Table 2 (continued)

Predictor ICU admission (*N.* Patients, %)	Yes = 140 (57.6)	No = 103 (42.4)	Odds ratio (OR) or Mean difference (MD)	95% CI	*p*-value	adjusted OR (aOR)	95% CI	*p*-value
Abdominal compartment syndrome (*N.* %)								
No	114 (81.4)	101 (98.1)	OR = 11.534	[2.672; 49.713]	< 0.001	6.214	[1.356; 28.490]	0.019
Yes	26 (18.6)	2 (1.9)						
Bleeding (*N.* %)								
No	104 (74.3)	96 (93.2)	OR = 4.754	[2.021; 11.234]	< 0.001	3.357	[1.373; 8.210]	0.008
Yes	36 (25.7)	7 (6.8)						
Bowel fistula (*N.* %)								
No	122 (87.1)	100 (87.1)	OR = 4.922	[1.413; 17.211]	0.006	2.009	[0.504; 8.000]	0.323
Yes	18 (12.9)	3 (12.9)						
Necrotizing cholecystitis (*N.* %)								
No	124 (88.6)	101 (98.1)	OR = 6.524	[1.461; 29.034]	0.005	2.794	[0.551; 14.160]	0.215
Yes	16 (11.4)	2 (1.9)						
Antibiotic therapy (*N.* %)								
No	13 (9.3)	22 (21.3)	OR = 2.651	[1.273; 5.564]	0.010	1.400	[0.630; 3.111]	0.408
Yes	127 (90.7)	81 (78.7)						
Antifungal therapy (*N.* %)								
No	70 (50.0)	83 (80.6)	OR = 4.153	[2.302; 7.491]	< 0.001	3.565	[1.920; 6.620]	< 0.001
Yes	70 (50.0)	20 (19.4)						
Total Parenteral Nutrition (*N.* %)								
No	84 (60.0)	75 (78.2)	OR = 1.793	[1.034; 3.101]	0.038	2.207	[1.067; 4.568]	0.033
Yes	56 (40.0)	28 (21.8)						
Enteral nutrition (*N.* %)								
No	81 (57.8)	65 (63.1)	OR = 0.803	[0.476; 1.353]	0.429	0.487	[0.245; 0.967]	0.040
Yes	59 (42.2)	38 (36.9)						

RAC Revised Atlanta Classification, *qSOFA* quick Sepsis-related Organ Failure Assessment, *BISAP* Bedside Index of Severity in Acute Pancreatitis, *APACHE II* Acute Physiology, Age, and Chronic Health Evaluation II, *ERCP/ES* Endoscopic Retrograde Cholangio-Pancreatography/Endoscopic Sphincterotomy, *WBC* white blood cells

Regarding comorbidities, a clinical history of diabetes ($p = 0.009$; OR 1.425) and arterial hypertension ($p < 0.001$; OR 2.954) were more frequent in non-survivors. qSOFA ($p = 0.002$; MD 1.003), BISAP (p = 0.002; MD 1.002), Glasgow-Imrie ($p = 0.043$; MD 1.003) and Ranson's scores ($p = 0.064$; MD 1.004) were higher in the non-survivors group. The non-survivors group had higher rates of severe AP ($p < 0.001$; OR 3.204), renal failure ($p < 0.001$; OR 3.901), haemodynamic failure ($p < 0.001$; OR 3.864), and respiratory failure ($p < 0.001$; OR 2.823) during hospital admission.

Concerning vital parameters, mean blood oxygen saturation ($p = 0.019$; MD 1.003) was higher in survivors, whereas respiratory rate ($p = 0.002$; MD 2.007) was lower. LDH ($p = 0.005$; MD 130) and CRP levels (p = 0.044; MD 1.401) differed between the survivors and non-survivors groups, with the latter showing higher levels.

Acute cholangitis was more common in non-survivor patients ($p = 0.004$; OR 2.793). ACS ($p < 0.001$; OR 4.725), gastrointestinal and/or intra-abdominal bleeding ($p < 0.001$; OR 3.623), bowel fistula ($p = 0.029$; OR 2.711), necrotising cholecystitis ($p = 0.002$; OR 4.712), and open surgical

Table 3 Results of the univariable and multivariable analyses. Outcome mortality

Predictor in-hospital mortality (*N*. Patients, %)	Yes = 58 (23.5)	No = 189 (76.5)	Odds Ratio (OR) or Mean Difference (MD)	95% CI	*p*-value	Adjusted OR (aOR)	95% CI	*p*-value
Sex (*N*. %)								
Male	30 (51.7)	105 (55.5)	OR = 0.852	[0.471; 1.552]	0.652			
Female	28 (48.3)	84 (44.5)						
Age (Years) Mean ± SD (Median; SE)	63.1 ± 16.3 (63.5; 2.15)	58.0 ± 17.2 (60.0; 1.25)	MD = 5.001	[10.023; – 4.351]	0.051	1.030	[1.002; 1.158]	0.034
COVID-19 Status on admission (*N*. %)								
Negative	52 (89.6)	179 (94.7)	OR = 2.073	[0.711; 5.953]	0.219			
Positive	6 (10.4)	10 (5.3)						
Previous episodes of biliary pancreatitis (*N*. %)								
No	36 (62.1)	117 (59.8)	OR = 0.750	[0.383; 1.451]	0.417			
Yes	22 (37.9)	72 (40.2)						
Admitting speciality (*N*. %)								
HPB Surgery	5 (8.6)	38 (20.1)	OR = 0.375	[0.140; 0.999]	0.044	0.164	[0.025; 1.052]	0.057
Other	53 (91.4)	151 (79.9)						
Setting of acquisition (N. %)								
Community acquired	50 (84.4)	170 (88.8)	OR = 1.525	[0.621; 3.721]	0.337			
Hospital acquired	8 (15.6)	19 (11.2)						
Charlson's Comorbidity Index Mean ± SD (Median; SE)	3.97 ± 4.55 (3.00; 0.59)	2.62 ± 2.40 (2.00; 0.17)	MD = 1.003	[– 2.002; – 4.261]	0.021	1.781	[1.505; 2.210]	0.269
Body Mass Index (BMI) Kg/m^2 Mean ± SD (Median; SE)	29.48 ± 6.12 (28.85; 0.94)	26.76 ± 5.79 (26.20; 0.54)	MD = 2.701	[– 4.803; – 0.801]	0.012	1.057	[0.976; 1.145]	0.172
Clinical history of diabetes (*N*. %)								
No	36 (62.1)	150 (79.3)	OR = 1.425	[1.222; 1.801]	0.009	0.717	[0.226; 2.272]	0.572
Yes	22 (37.9)	39 (20.7)						
Clinical history of chronic pulmonary disease (*N*. %)								
No	46 (79.3)	165 (87.3)	OR = 1.796	[0.836; 3.861]	0.140			
Yes	12 (20.7)	24 (12.7)						
Clinical history of hypertension (*N*. %)								
No	16 (27.6)	100 (52.9)	OR = 2.954	[1.553; 5.612]	< 0.001	4.245	[1.135; 15.882]	0.032
Yes	42 (72.4)	89 (47.1)						
Clinical history of atrial fibrillation (*N*. %)								

Table 3 (continued)

Predictor in-hospital mortality (*N*. Patients, %)	Yes = 58 (23.5)	No = 189 (76.5)	Odds Ratio (OR) or Mean Difference (MD)	95% CI	*p*-value	Adjusted OR (aOR)	95% CI	*p*-value
No	51 (87.9)	167 (88.3)	OR = 1.047	[0.421; 2.581]	0.929			
Yes	7 (12.1)	22 (11.7)						
Clinical history of ischaemic heart disease (*N*. %)								
No	50 (86.2)	170 (89.9)	OR = 1.434	[0.593; 3.473]	0.471			
Yes	8 (13.8)	19 (10.1)						
Clinical history of chronic kidney disease (*N*. %)								
No	52 (89.6)	181 (95.7)	OR = 2.615	[0.862; 7.865]	0.078			
Yes	6 (10.4)	8 (4.3)						
Clinical history of diseases of the hematopoietic system (N. %)								
No	57 (98.3)	184 (97.3)	OR = 0.646	[0.071; 5.645]	0.690			
Yes	1 (1.7)	5 (2.7)						
Patient on immunosuppressive medications (*N*. %)								
No	57 (98.3)	180 (95.2)	OR = 0.351	[0.041; 2.831]	0.460			
Yes	1 (1.7)	9 (4.8)						
qSOFA Mean ± SD (Median; SE)	1.36 ± 0.98 (1.00; 0.15)	0.81 ± 1.01 (0.00; 0.09)	MD = 1.003	[– 1.001; – 2.372]	0.002	2.828	[1.359; 5.879]	0.005
BISAP score Mean ± SD (Median; SE)	2.48 ± 1.20 (3.00; 0.18)	1.95 ± 1.59 (2.00; 0.16)	MD = 1.002	[– 1.004; – 5.461]	0.002	0.792	[0.461; 1.360]	0.399
Glasgow-Imrie criteria Mean ± SD (Median; SE)	3.26 ± 1.42 (3.00; 0.24)	2.70 ± 1.67 (2.00; 0.17)	MD = 1.003	[– 1.002; – 3.701]	0.043	1.197	[0.697; 2.056]	0.514
Ranson's criteria Mean ± SD (Median; SE)	3.33 ± 1.47 (3.00; 0.24)	2.78 ± 1.65 (2.00; 0.16)	MD = 1.004	[– 1.003; 1.202]	0.064			
APACHE II score Mean ± SD (Median; SE)	9.20 ± 5.49 (8.50; 1.00)	7.60 ± 5.10 (7.00; 0.59)	MD = 2.001	[– 3.001; 1.001]	0.175			
Revised Atlanta Classification (RAC) stage (*N*. %)								
Moderately severe	18 (31.1)	49 (25.9)	OR = 1.293	[0.671; 2.452]	0.444			
Severe	34 (58.6)	58 (30.7)	OR = 3.204	[1.742; 5.871]	< 0.001	2.114	[0.595; 7.512]	0.247
APACHE II score Mean ± SD (Median; SE)	9.20 ± 5.49 (8.50; 1.00)	7.60 ± 5.10 (7.00; 0.59)	MD = 2.001	[– 3.001; 1.001]	0.175			
Revised Atlanta Classification (RAC) stage (*N*. %)								

Table 3 (continued)

Predictor in-hospital mortality (*N*. Patients, %)	Yes = 58 (23.5)	No = 189 (76.5)	Odds Ratio (OR) or Mean Difference (MD)	95% CI	*p*-value	Adjusted OR (aOR)	95% CI	*p*-value
Moderately severe	18 (31.1)	49 (25.9)	OR = 1.293	[0.671; 2.452]	0.444			
Severe	34 (58.6)	58 (30.7)	OR = 3.204	[1.742; 5.871]	< 0.001	2.114	[0.595; 7.512]	0.247
Organ failure during the hospital admission (*N*. %)								
No	4 (6.9)	114 (66.2)	OR = 13.443	[4.653; 38.411]	< 0.001	11.589	[3.873; 34.671]	< 0.001
Yes	54 (93.1)	64 (33.8)						
Renal failure during the hospital admission (*N*. %)								
No	27 (46.5)	146 (77.2)	OR = 3.901	[2.101; 7.231]	< 0.001	2.489	[1.138; 5.442]	0.022
Yes	31 (53.5)	43 (22.8)						
Haemodynamic failure during the hospital admission (*N*. %)								
No	33 (56.9)	158 (83.6)	OR = 3.864	[2.022; 7.371]	< 0.001	2.661	[1.184; 5.978]	0.018
Yes	25 (43.1)	31 (16.4)						
Respiratory failure during the hospital admission (*N*. %)								
No	28 (48.3)	137 (72.5)	OR = 2.823	[1.541; 5.171]	< 0.001	2.033	[0.906; 4.560]	0.085
Yes	30 (51.7)	52 (27.5)						
Temperature on admission °C Mean ± SD (Median; SE)	36.8 ± 2.31 (37.0; 0.30)	36.9 ± 0.89 (36.8; 0.06)	MD = 9.513	[– 0.403; 0.202]	0.656			
Systolic blood pressure on admission (mmHg) Mean ± SD (Median; SE)	117 ± 27.2 (110; 3.57)	127 ± 49.1 (120; 3.57)	MD = 8.004	[– 8.101; 15.023]	0.054			
Heart rate on admission (bpm) Mean ± SD (Median; SE)	95.9 ± 17.8 (97.0; 2.33)	90.9 ± 18.7 (88.5; 1.36)	MD = 5.031	[– 10.522; 0.421]	0.071			
Respiratory rate on admission (breaths/min) Mean ± SD (Median; SE)	20.3 ± 3.74 (20.0; 0.49)	18.6 ± 4.17 (18.0; 0.30)	MD = 2.007	[– 3.001; – 1.001]	0.002	1.078	[0.998; 1.163]	0.056
Blood oxygen saturation level (SpO_2%) on admission Mean ± SD (Median; SE)	93.9 ± 4.68 (95.0; 0.61)	95.4 ± 3.44 (96.0; 0.25)	MD = 1.003	[1.642; 2.001]	0.019	0.938	[0.869; 1.010]	0.098

Table 3 (continued)

Predictor in-hospital mortality (*N*. Patients, %)	Yes = 58 (23.5)	No = 189 (76.5)	Odds Ratio (OR) or Mean Difference (MD)	95% CI	*p*-value	Adjusted OR (aOR)	95% CI	*p*-value
WBC on admission (cells/mm^3) Mean ± SD (Median; SE)	17.7 ± 7.13 (17.5; 0.94)	16.7 ± 6.28 (16.7; 0.47)	MD = 1.071	[– 3.021; 0.881]	0.281			
Neutrophils on admission (cells/mm^3) Mean ± SD (Median; SE)	14.9 ± 7.03 (14.2; 1.00)	13.8 ± 5.80 (13.7; 0.45)	MD = 0.601	[– 2.503; 1.401]	0.570			
Platelets on admission (mcL) Mean ± SD (Median; SE)	256 ± 137 (229; 18.3)	270 ± 127 (255; 9.59)	MD = 17.045	[– 17.034; 53.012]	0.309			
INR—International Normalised Ratio on admission Mean ± SD (Median; SE)	1.48 ± 0.80 (1.25; 0.10)	1.33 ± 0.58 (1.17; 0.04)	MD = 0.063	[– 0.181; 0.011]	0.122			
CRP—C-reactive Protein on admission (mg/L) Mean ± SD (Median; SE)	126 ± 129 (59.0; 20.0)	119 ± 124 (73.8; 9.96)	MD = 1.401	[– 24.011; 22.321]	0.848	1.010	[1.023; 1.103]	0.044
AST—Aspartate aminotransferase on admission (U/L) Mean ± SD (Median; SE)	199 ± 181 (138; 26.2)	173 ± 185 (101; 15.5)	MD = 18.023	[– 60.023; 14.011]	0.268			
ALT—Alanine aminotransferase on admission (U/L) Mean ± SD (Median; SE)	237 ± 325 (142; 44.6)	208 ± 273 (96.0; 20.8)	MD = 13.012	[– 57.021; 19.032]	0.489			
Total Bilirubin on admission (mg/dL) Mean ± SD (Median; SE)	2.62 ± 2.48 (1.79; 0.33)	2.66 ± 2.69 (1.60; 0.20)	MD = 2.014	[– 0.361; 0.401]	0.959			
Conjugated Bilirubin on admission (mg/dL) Mean ± SD (Median; SE)	1.72 ± 1.94 (0.91; 0.28)	1.47 ± 1.52 (0.91; 0.14)	MD = 4.796	[– 0.302; 0.294]	0.957			
Serum Amylase on admission (U/L) Mean ± SD (Median; SE)	1585 ± 1460 (901; 223)	1426 ± 1437 (905; 121)	MD = 47.034	[– 302; 165]	0.553			
Serum Lipase on admission (U/L) Mean ± SD (Median; SE)	3201 ± 4155 (1499; 683)	2772 ± 3349 (1264; 300)	MD = 83.022	[– 640; 367]	0.671			

Table 3 (continued)

Predictor in-hospital mortality (*N*. Patients, %)	Yes = 58 (23.5)	No = 189 (76.5)	Odds Ratio (OR) or Mean Difference (MD)	95% CI	*p*-value	Adjusted OR (aOR)	95% CI	*p*-value
LDH—Lactate DeHydrogenase on admission (U/L) Mean ± SD (Median; SE)	746 ± 823 (495; 133)	439 ± 245 (384; 25.9)	MD = 130.243	[– 218; – 46.0]	0.005	1.007	[1.001; 1.011]	0.006
Procalcitonin on admission (ng/mL) Mean ± SD (Median; SE)	4.42 ± 6.14 (2.32; 1.31)	3.50 ± 6.55 (1.41; 0.91)	MD = 1.0432	[– 2.101; 0.222]	0.118			
Lactates on admission (mmol/L) Mean ± SD (Median; SE)	2.51 ± 1.47 (2.15; 0.28)	2.69 ± 1.56 (2.25; 0.16)	MD = 0.1001	[– 0.403; 0.701]	0.598			
Diffuse abdominal pain (N. %)								
No	25 (43.1)	93 (49.2)	OR = 0.782	[0.431; 1.411]	0.416			
Yes	33 (56.9)	96 (50.8)						
Diffuse abdominal rigidity (*N*. %)								
No	44 (75.8)	153 (80.9)	OR = 0.739	[0.362; 1.493]	0.399			
Yes	14 (24.2)	36 (19.1)						
Concomitant choledocholithiasis (*N*. %)								
No	24 (41.4)	130 (68.8)	OR = 1.563	[0.841; 2.851]	0.152			
Yes	34 (58.6)	59 (31.2)						
Concomitant common bile duct obstruction (*N*. %)								
No	52 (89.6)	171 (90.5)	OR = 1.101	[0.412; 2.913]	0.804			
Yes	6 (10.4)	18 (9.5)						
Concomitant acute cholangitis (*N*. %)								
No	43 (74.1)	168 (88.9)	OR = 2.793	[1.332; 5.862]	0.004	3.983	[1.598; 9.930]	0.003
Yes	15 (25.9)	21 (11.1)						
ERCP/ES > 48 h for concomitant choledocholithiasis, common bile duct obstruction, or cholangitis (*N*. %)								
No	19 (67.8)	48 (76.2)	OR = 1.521	[0.561; 4.051]	0.405			
Yes	9 (32.2)	15 (23.8)						

Table 3 (continued)

Predictor in-hospital mortality (*N*. Patients, %)	Yes = 58 (23.5)	No = 189 (76.5)	Odds Ratio (OR) or Mean Difference (MD)	95% CI	*p*-value	Adjusted OR (aOR)	95% CI	*p*-value
ERCP/ES ≤ 48 h for concomitant choledocholithiasis, common bile duct obstruction, or cholangitis (*N*. %)								
No	17 (44.7)	35 (55.5)	OR = 0.809	[0.324; 2.002]	0.646			
Yes	11 (55.3)	28 (44.5)						
Endoscopic step-up drainage of pancreatic necrosis (*N*. %)								
No	50 (86.2)	141 (74.6)	OR = 0.475	[0.203; 1.061]	0.064	0.339	[0.138; 0.834]	0.018
Yes	8 (13.8)	48 (17.9)						
Upfront open surgical necrosectomy (*N*. %)								
No	37 (63.8)	151 (82.1)	OR = 3.233	[1.723; 6.051]	< 0.001	3.772	[1.912; 7.442]	< 0.001
Yes	21 (36.2)	33 (20.1)						
Percutaneous drainage/minimally invasive necrosectomy (*N*. %)								
No	53 (91.4)	173 (91.5)	OR = 1.021	[0.352; 2.923]	0.970			
Yes	5 (8.6)	16 (8.5)						
Surgical necrosectomy < 2 weeks from the onset (*N*. %)								
No	25 (67.6)	41 (68.3)	OR = 1.043	[0.432; 2.491]	0.937			
Yes	12 (32.4)	19 (31.7)						
Surgical necrosectomy 2–4 weeks from the onset (*N*. %)								
No	21 (59.7)	45 (81.8)	OR = 2.293	[0.954; 5.481]	0.061	1.689	[0.616; 4.633]	0.309
Yes	14 (40.3)	10 (18.2)						
Surgical necrosectomy > 4 weeks from the onset (*N*. %)								
No	28 (77.7)	34 (60.7)	OR = 2.384	[0.953; 5.901]	0.081	0.234	[0.075; 0.724]	0.012
Yes	8 (22.3)	22 (39.3)						
Abdominal compartment syndrome (*N*. %)								
No	43 (74.1)	176 (93.1)	OR = 4.725	[2.092; 10.734]	< 0.001	2.735	[1.090; 6.867]	0.032
Yes	15 (25.9)	13 (6.9)						

Table 3 (continued)

Predictor in-hospital mortality (*N*. Patients, %)	Yes = 58 (23.5)	No = 189 (76.5)	Odds Ratio (OR) or Mean Difference (MD)	95% CI	*p*-value	Adjusted OR (aOR)	95% CI	*p*-value
Bleeding (*N*. %)								
No	38 (65.5)	165 (87.3)	OR = 3.623	[1.811; 7.221]	< 0.001	2.710	[1.286; 5.712]	0.009
Yes	20 (34.5)	24 (12.7)						
Bowel fistula (*N*. %)								
No	49 (84.5)	177 (93.6)	OR = 2.711	[1.081; 6.803]	0.029	1.085	[0.366; 3.211]	0.884
Yes	9 (15.5)	12 (6.4)						
Necrotizing cholecystitis (*N*. %)								
No	48 (82.7)	181 (95.7)	OR = 4.712	[1.761; 12.634]	0.002	2.669	[0.875; 8.141]	0.084
Yes	10 (17.3)	8 (4.3)						
Antibiotic therapy (*N*. %)								
No	7 (12.1)	28 (14.8)	OR = 1.271	[0.521; 3.073]	0.673			
Yes	51 (87.9)	161 (85.2)						
Antifungal therapy (*N*. %)								
No	33 (56.9)	123 (65.1)	OR = 1.411	[0.771; 2.571]	0.258			
Yes	25 (43.1)	66 (34.9)						
Total Parenteral Nutrition (*N*. %)								
No	33 (56.9)	129 (68.2)	OR = 1.633	[0.893; 2.981]	0.117	0.821	[0.391; 1.722]	0.602
Yes	25 (43.1)	60 (31.8)						
Enteral nutrition (*N*. %)								
No	45 (77.5)	105 (55.5)	OR = 0.361	[0.183; 0.711]	0.003	0.320	[0.143; 0.716]	0.006
Yes	13 (22.5)	84 (44.5)						

HPB Hepato-Pancreato-Biliary, *RAC* Revised Atlanta Classification, *qSOFA* quick Sepsis-related Organ Failure Assessment, *BISAP* Bedside Index of Severity in Acute Pancreatitis, *APACHE II* Acute Physiology, Age, and Chronic Health Evaluation II, *ERCP/ES* Endoscopic Retrograde Cholangio-Pancreatography/Endoscopic Sphincterotomy, *WBC* White Blood Cells

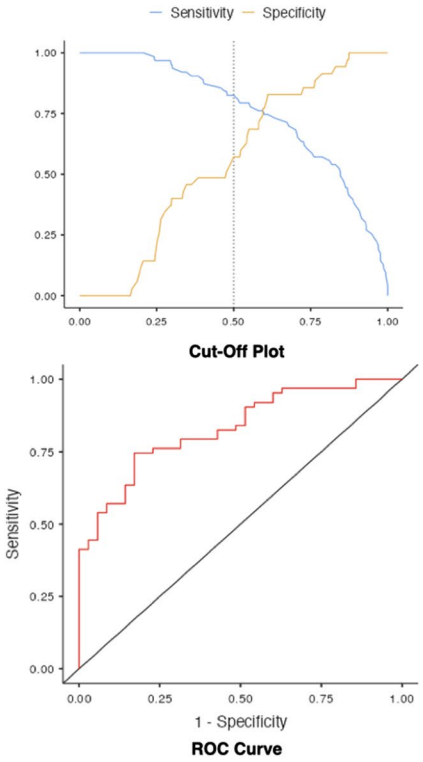
necrosectomy ($p < 0.001$; OR 3.233) were associated with higher mortality. Being admitted to an HPB surgery department ($p = 0.044$; OR 0.375) and the administration of enteral nutrition ($p = 0.003$; OR 0.361) were protective factors against in-hospital mortality.

Details of the final multivariable prediction model for the risk of mortality in IPN patients are shown in Table 3.

In the multivariable logistic regression analysis, age ($p = 0.034$; aOR 1.030), history of uncontrolled arterial hypertension ($p = 0.032$; aOR 4.245), qSOFA (p = 0.005; aOR 2.828), organ failure ($p < 0.001$; aOR 11.589), renal failure ($p = 0.022$; aOR 2.489), haemodynamic failure (p = 0.018; aOR 2.661), CRP ($p = 0.044$; aOR 1.010), LDH ($p = 0.006$; aOR 1.007), acute cholangitis ($p = 0.003$; aOR 3.983), ACS (p = 0.032; aOR 2.735), gastrointestinal and/or intra-abdominal bleeding ($p = 0.009$; aOR 2.710) and upfront open surgical necrosectomy ($p < 0.001$; aOR 3.772) were identified as independent predictors of mortality. Endoscopic drainage of pancreatic necrosis ($p = 0.018$; aOR 0.339) and delayed (> 4 weeks) necrosectomy ($p = 0.012$; aOR 0.234) were found as protective factors against mortality in the multivariable analysis.

The optimal cut-point was for CRP 125 mg/L (Sensitivity 81.94%, Specificity 38.57%, PPV 80.89%, NPV 40.2%, Accuracy 72.6%), age 76 years (Sensitivity 79.73%, Specificity 39.87%, PPV 82.76%, NPV 30.3%, Accuracy 77.5%), and LDH 510 U/L (Sensitivity 39.21%, Specificity 55.26%, PPV 60.47%, NPV 38.2%, Accuracy 52.3%).

ROC curves were plotted to assess the performance of the combination of the parameters mentioned above to predict mortality in this group of patients. The results of the ROC analysis are shown in Fig. 3. The final results of the stepwise multivariable logistic regression for mortality in patients with IPN (logistic regression X^2 20.4; $p = 0.037$; pseudo R^2 0.309; Nagelkerke R^2 0.423; McFadden's R^2



Body Mass Index (BMI)	p= 0.015	cut-point 34 Kg/m2	adjusted OR 1.071
Diabetes	p< 0.001		adjusted OR 1.356
Respiratory failure	p< 0.001		adjusted OR 6.899
Blood oxygen saturation level	p< 0.001	cut-point 91%	adjusted OR 1.844
Lactate DeHydrogenase (LDH)	p= 0.010	cut-point 554 U/L	adjusted OR 1.005
Diffuse abdominal rigidity	p= 0.002		adjusted OR 3.727
Upfront surgical necrosectomy	p< 0.001		adjusted OR 5.362
Abdominal Compartment Syndrome	p< 0.001		adjusted OR 6.214
Total parenteral nutrition	p= 0.038		adjusted OR 2.207

Accuracy	**Specificity**	**Sensitivity**	**AUC**
0,724	0,571	0,810	0,830

Fig. 2 Intensive care unit (ICU) admission prediction model

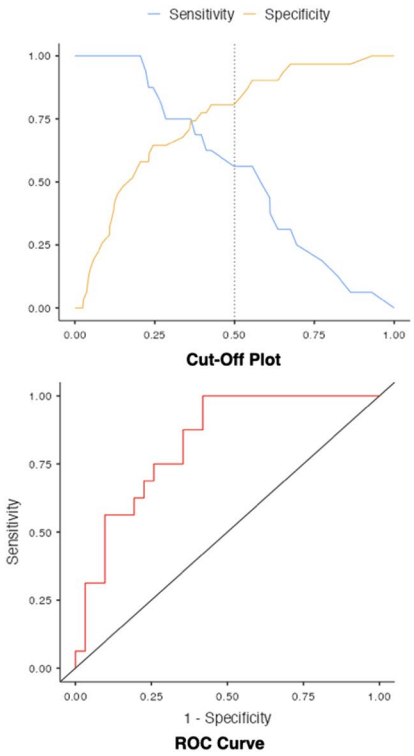
0.282) consisted of 11 variables. Calibration of the model determined quantitatively by the Hosmer–Lemeshow goodness of fit statistics (LH X^2 3.04, $p = 0.067$) confirmed that the model could assign appropriate risk among the patients whose experience is simulated by the model. As a result of discrimination evaluated using ROC analysis, the model's accuracy was 74.5%, specificity was 83.9%, and sensitivity was 56.3%, with an AUROC = 0.829.

Discussion

In this post hoc analysis of the MANCTRA-1 study, we have shown that the adverse outcomes in patients with IPN are related to two separate groups of factors. On the one hand, we found factors related to the disease course and its severity, such as organ failure, acute cholangitis, and abdominal compartment syndrome, or to the patient's comorbidity, such as obesity, diabetes, and uncontrolled arterial hypertension. On the other, we found modifiable factors related to patient management. In particular, when the current guidelines and recommendations are not followed, for example, in the cases of upfront open surgical necrosectomy or when nutritional support is provided via total parenteral nutrition instead of enteral nutrition.

While in previous studies [28, 29] predictive variables were assessed to identify early determinants of pancreatic necrosis and organ failure, we implemented our research intending to assess the risk of mortality early in the course of the disease in patients with confirmed IPN.

Although patient-specific risk algorithms have been implemented in previous studies with evidence of benefit in improving the prediction of patient outcomes, it is still undetermined what factors can impact the survival once infection of pancreatic necrosis has been established [30]. In this post hoc analysis of the MANCTRA-1 study, the association of age > 76 years, history of uncontrolled arterial hypertension, CRP > 125 mg/L, LDH > 510 U/L, renal failure, haemodynamic failure and acute cholangitis diagnosed within 72 h from hospital admission allowed to predict mortality. Moreover, by adding the occurrence of necrosectomy performed with open technique, ACS and intra-abdominal bleeding later in the course of the disease, the model could predict mortality with an accuracy of 74.5%. Within this context, the most relevant and potentially modifiable factors to reduce mortality were early haemodynamic and renal support, managing cholangitis with ERCP/ES ≤ 48 h from hospital admission, providing enteral nutrition, and reserving open necrosectomy to patients for whom the minimally invasive and endoscopic step-up approaches have failed to



CRP	p= 0.044	cut-point 125 mg/L	adjusted OR 1.010
LDH	p= 0.006	cut-point 510 U/L	adjusted OR 1.007
Age	p= 0.034	cut-point 76 years	adjusted OR 1.030
Arterial hypertension	p= 0.032		adjusted OR 4.245
qSOFA	p= 0.005		adjusted OR 2.828
Renal failure	p= 0.022		adjusted OR 2.489
Haemodynamic failure	p= 0.018		adjusted OR 2.661
Acute cholangitis	p= 0.003		adjusted OR 3.983
Abdominal Compartment Syndrome	p= 0.032		adjusted OR 2.735
Upfront open surgery	p< 0.001		adjusted OR 3.772
Bleeding	p= 0.009		adjusted OR 2.710

Accuracy	Specificity	Sensitivity	AUC
0,745	0,839	0,563	0,829

Fig. 3 Mortality prediction model

improve clinical conditions. These strategies are currently supported by several clinical guidelines [20, 21].

Previous studies focusing on patients with IPN found that multiple organ failure, long duration (≥ 5 days) of organ failure, and open necrosectomy performed outside a step-up approach were associated with high mortality rates [31]. Similarly, in an extensive systematic review and meta-analysis, Werge et al. [8] found that patients with IPN were more than twice as likely to die compared to patients with sterile necrosis. In this setting, the timing of organ failure is essential. In our study, organ failure was detected early in the course of the disease (within 72 h of hospital admission), which can be of absolute relevance in terms of prognosis. In the study by Singh et al. [32], among 300 patients with necrotising pancreatitis, 58% had organ failure, in keeping with what we found in our study (62%). The highest mortality was noted in patients with organ failure persisting for longer than three weeks. Moreover, among patients with multiple organ failure, those with multiple sequential failures had a worse outcome than those with simultaneous failures. Unfortunately, in our study, we could not assess if the association of two or more types of organ failure was concomitant or sequential. However, the logistic regression analysis confirmed organ failure as a significant predictor of mortality. Among all types of organ failure, our study showed that renal failure and haemodynamic failure, more than respiratory, were strong predictors of mortality in patients with IPN.

IPN is a disease that mandates individual patient evaluation in a multidisciplinary setting in collaboration among gastroenterologists, surgeons, endoscopists, intensive care physicians, and interventional radiologists, to adequately evaluate patients' suitability for different available interventions and treatment options. Guidelines recommend that interventional strategies in patients with pancreatic necrosis should be delayed until necrosis is well demarcated [20, 21]. Demarcation facilitates necrosectomy and reduces complications related to drainage and debridement procedures, justifying the recent shift in current practice toward a minimally invasive step-up approach [33, 34]. The PANTER randomised trial by van Santvoort et al. [12] showed the advantages of the step-up approach compared to primary open necrosectomy for patients with IPN included lower rates of long-term complications and new-onset organ failure, and less health care resource utilisation. Moreover, in the same study, 35% of patients were successfully treated with percutaneous drainage alone and did not require surgical necrosectomy. It is well established that minimally invasive treatment strategies cause less surgical trauma, including less tissue injury and proinflammatory response in patients who are already severely ill [15]. In clinical practice, this relates to a substantial reduction in the incidence of new-onset multiple organ failure in patients

treated with a surgical or endoscopic step-up approach [12, 35, 36]. However, up to 45% of patients treated with a surgical step-up approach develop pancreatico-cutaneous fistulas after percutaneous catheter drainage or minimally invasive necrosectomy as the second step [37, 38]. This is why we are currently witnessing a shift to the endoscopic step-up approach as a treatment preference of IPN whenever possible [39]. In our study, only 22.7% of patients underwent IPN drainage within a step-up endoscopic approach while, contrary to what is recommended by current guidelines, 61.3% underwent upfront open surgical necrosectomy without passing through a step-up strategy. Furthermore, 36.0% of patients who underwent surgical necrosectomy did it in the timing > 4 weeks and 64.0% before four weeks. In our multivariable analysis, while endoscopic drainage of pancreatic necrosis within a step-up approach (aOR 0.339) and delayed (> 4 weeks) necrosectomy (aOR 0.234) were found protective against mortality risk, upfront surgical necrosectomy was associated with four-time increased mortality. Our results were in keeping with previous studies demonstrating that early open surgery is a clear determinant of death risk. At the same time, minimally invasive interventions through a step-up approach, including percutaneous or endoscopic drainage, do not appear to affect mortality [39–41].

Finally, the findings of our study proved that enteral nutrition significantly reduced the risk of ICU admission and the mortality rate. Our results are consistent with some previous data demonstrating the beneficial effect of enteral nutrition over total parenteral nutrition [42]. However, unlike previous studies, we could not assess the effect of enteral nutrition starting at different time points. Patients with severe AP are vulnerable to many potential risk factors associated with the development of pancreatic and/or peri-pancreatic and systemic infections, and receiving total parenteral nutrition has shown to be associated with the risk of developing multi-drug resistant infective complications [43, 44]. Based on these potential advantages, American and European scientific societies of pancreatology currently recommend routine early enteral feeding in all patients with severe AP when patients cannot tolerate an oral diet [21, 45].

Strengths and limitations

We acknowledge some limitations in this study, mainly related to the retrospective nature of the analysis.

The MANCTRA-1 study included centres having different levels of experience in treating AP. So, it is possible that the risks associated with infections and mortality were more significant if the patients were managed at centres with more limited experience, mainly when critically ill patients were not referred to specialist HPB units. This study was also limited by the variability in practice, different indications for surgical intervention, and quality of the prognostic modelling strategies due to the low adherence level to guidelines recommendations, as demonstrated in our previous audit [24]. These may have introduced the possibility of selection bias.

Nevertheless, the results of our study underlined that the best outcomes in patients with IPN are achieved when the guidelines are followed and that, as for other conditions, the discrepancy between what is recommended and the current daily practice is often significant.

Finally, there is a residual chance of having missed relevant variables, especially those showing a dynamic evolution during the course of the disease. However, there are also several strengths of the present study. First, the strict inclusion criteria of patients with IPN ensured homogeneity in the study population, whereas previous studies looking at different interventions enrolled both infected and non-infected pancreatic collections, which are associated with different mortality rates. Moreover, as a multinational study with 150 participating centres across 41 different countries, the generalisability of our study results is high. Finally, our study emphasised two relevant issues: the need for evidence-based standardisation of the management of IPN and the importance of a timely referral to a specialist unit for patients with extensive necrotizing forms who may require ICU care and 24-h interventional radiological, endoscopic, or HPB surgical services. Indeed, managing patients with IPN involves the availability of many specialty services (gastroenterology, interventional endoscopy, surgery, critical care, and interventional radiology) and the experience of coordinating a multidisciplinary team. Therefore, if the full range of specialists is unavailable in the receiving hospital, a nominated team for managing severe AP patients should coordinate local treatments, where possible, and the referral to a specialist unit where appropriate.

Conclusions

The results of this post hoc analysis of the MANCTRA-1 study can help overcome current limitations in identifying patients with IPN at the highest risk of death, ultimately leading to early identification of the patients requiring major clinical and interventional efforts. Organ failure (aOR 11.589), acute cholangitis (aOR 3.983), and open surgical necrosectomy (aOR 3.772) were the most significant predictors of mortality. Our study confirmed that, even in a subgroup of particularly ill patients such as those with IPN, upfront open surgery should be avoided as much as possible, as it is a clear determinant of death. Conversely,

minimally invasive surgical and endoscopic interventions through a step-up approach should be attempted at the first stage. Patients with IPN should be referred to a specialised centre and taken into a high-dependency or intensive care unit as early as possible.

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Ethical approval The study met and conformed to the standards outlined in the principles of the Declaration of Helsinki of 1975 (as revised in 2008) and was conducted following the ethical standards of the responsible committee on human experimentation (Independent Ethical Committee for Clinical Trials of Cagliari University Hospital, Italy). Ethics Committee approval was obtained from the coordinating centre in Italy (Acceptance Code: Independent Ethics Committee of the University of Cagliari, Prot. P.G./2021/7108). All the investigators conducted the study according to the rules of the local ethics committee regarding the retrospective collection of data.

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