coMpliAnce with evideNce-based cliniCal guidelines in the managemenT of acute biliaRy pancreAtitis): The MANCTRA-1 international audit☆

Mauro Podda [a,*], Daniela Pacella [b], Gianluca Pellino [c,d], Federico Coccolini [e], Alessio Giordano [f], Salomone Di Saverio [g], Francesco Pata [h], Benedetto Ielpo [i], Francesco Virdis [j], Dimitrios Damaskos [k], Belinda De Simone [l], Ferdinando Agresta [m], Massimo Sartelli [n], Ari Leppaniemi [o], Cristiana Riboni [p], Vanni Agnoletti [q], Damian Mole [r], Yoram Kluger [s], Fausto Catena [t], Adolfo Pisanu [a], the MANCTRA-1 Collaborative Group, Principal Investigator, Steering Committee, MANCTRA-1 Coordinating Group, Local Collaborators, Argentina, Australia, Bahrain, Brazil, Bulgaria, China, Colombia, Czech Republic, Egypt, France, Georgia, Greece, Guatemala, India, Italy, Jordan, Malaysia, Mexico, Nigeria, Pakistan, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia, Serbia, Slovak Republic, South Africa, Spain, Sudan, Switzerland, Syria, Tunisia, Turkey, United Kingdom, Uruguay, Yemen

[a] *Department of Surgical Science, Emergency Surgery Unit, University of Cagliari, Cagliari, Italy*
[b] *University of Naples Federico II, Department of Public Health, Naples, Italy*
[c] *'Luigi Vanvitelli' University of Campania, Naples, Italy*
[d] *Colorectal Surgery, Vall d'Hebron University Hospital, Barcelona, Spain*
[e] *General, Emergency and Trauma Surgery Unit, Pisa University Hospital, Pisa, Italy*
[f] *Department of General Surgery, Santo Stefano Hospital, Prato, Italy*
[g] *Department of Surgery, Madonna del Soccorso Hospital, San Benedetto del Tronto, Italy*
[h] *General Surgery Unit, Nicola Giannettasio Hospital, Corigliano-Rossano, Italy*
[i] *HPB Surgery Unit, Hospital del Mar, Barcelona, Spain*
[j] *Trauma and Acute Care Surgery Unit, Niguarda Ca Granda Hospital, Milan, Italy*
[k] *Department of Upper GI Surgery, Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK*
[l] *Department of Emergency and Metabolic Minimally Invasive Surgery, Centre Hospitalier Intercommunal de Poissy/Saint Germain en Laye, Poissy Cedex, France*
[m] *Department of Surgery, Vittorio Veneto Civil Hospital, Vittorio Veneto, Italy*
[n] *Department of Surgery, Macerata Civil Hospital, Macerata, Italy*
[o] *Department of Abdominal Surgery, Abdominal Center, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland*
[p] *Department of Surgery, EOC Regional Hospital, Lugano, Switzerland*
[q] *Intensive Care Unit, Bufalini Hospital, Cesena, Italy*
[r] *Centre for Inflammation Research, Clinical Surgery, University of Edinburgh, Edinburgh, Scotland, UK*
[s] *Division of General Surgery, Rambam Health Care Campus, Haifa, Israel*
[t] *Department of Emergency and Trauma Surgery, Bufalini Hospital, Cesena, Italy*

ARTICLE INFO

Article history:
Received 17 May 2022
Received in revised form
24 June 2022

ABSTRACT

Background/objectives: Reports about the implementation of recommendations from acute pancreatitis guidelines are scant. This study aimed to evaluate, on a patient-data basis, the contemporary practice patterns of management of biliary acute pancreatitis and to compare these practices with the recommendations by the most updated guidelines.

☆ Part of this study was presented during the 8th International Congress of the World Society of Emergency Surgery (Edinburgh, UK, 7–10 September 2021), and it is currently under evaluation for oral presentation during the United European Gastroenterology week 2022 (Vienna, 8–11 October 2022).

* Corresponding author. Department of Surgical Science, University of Cagliari Emergency Surgery Unit, Policlinico Universitario "D. Casula", Azienda Ospedaliero-Universitaria di Cagliari SS 554, Km 4, 500 09042, Monserrato, Italy. Tel.: +3907051096571
E-mail address: mauro.podda@unica.it (M. Podda).

Keywords:
Acute pancreatitis
Biliary pancreatitis
Global surgery
Guidelines compliance
International audit

Methods: All consecutive patients admitted to any of the 150 participating general surgery (GS), hepatopancreatobiliary surgery (HPB), internal medicine (IM) and gastroenterology (GA) departments with a diagnosis of biliary acute pancreatitis between 01/01/2019 and 31/12/2020 were included in the study. Categorical data were reported as percentages representing the proportion of all study patients or different and well-defined cohorts for each variable. Continuous data were expressed as mean and standard deviation. Differences between the compliance obtained in the four different subgroups were compared using the Mann-Whitney U, Student's *t*, ANOVA or Kruskal-Wallis tests for continuous data, and the Chi-square test or the Fisher's exact test for categorical data.
Results: Complete data were available for 5275 patients. The most commonly discordant gaps between daily clinical practice and recommendations included the optimal timing for the index CT scan (6.1%, χ^2 6.71, $P = 0.081$), use of prophylactic antibiotics (44.2%, χ^2 221.05, $P < 0.00001$), early enteral feeding (33.2%, χ^2 11.51, $P = 0.009$), and the implementation of early cholecystectomy strategies (29%, χ^2 354.64, $P < 0.00001$), with wide variability based on the admitting speciality.
Conclusions: The results of this study showed an overall poor compliance with evidence-based guidelines in the management of ABP, with wide variability based on the admitting speciality.
Study protocol registered in ClinicalTrials.Gov (ID Number NCT04747990).

What is already known on this topic. Acute pancreatitis is still associated with considerable adverse outcomes, with published overall mortality reaching up to 7%. When compliance studies have been performed on single national cohorts, their results have generally been unsatisfactory.

What this study adds. This study highlights discordant gaps between daily clinical practice and recommendations from pancreatitis guidelines, including the use of prophylactic antibiotics, early oral feeding or enteral feeding, and the implementation of early cholecystectomy strategies to minimise the rate of hospital readmission and recurrent episodes of pancreatitis.

How this study might affect research, practice or policy. Having regard to the overall poor compliance with guidelines highlighted by this study, these results will be analysed to provide the basis for introducing a number of bundles in ABP patients' management to be disseminated during the following years.

1. Introduction

Acute pancreatitis (AP) is still associated with considerable adverse outcomes, with published overall mortality reaching up to 2% in Western countries [1–4] and 7.5% in Asia [5]. Many scientific societies have issued practice guidelines over the past decades to guide surgeons and physicians in managing AP [6–11]. However, reports about the real-world implementation of evidence-based recommendations coming from AP guidelines are scant [12–17].

Implementation of guidelines is more difficult the more interventional is the key recommendation and when the recommendation depends on factors not readily controlled by the admitting specialists [18]. Acute biliary pancreatitis (ABP) can benefit from reduced risk of further attacks through early definitive surgical or endoscopic intervention. Patients with mild ABP should undergo definitive treatment of the biliary tract during the same hospital admission or within two weeks of discharge [19]. Adherence to this pathway improves patient outcomes, reduces overall hospital stay and healthcare costs and, most important, decreases the incidence of recurrent ABP [20,21].

The identification of the areas of sub-optimal care due to the lack of compliance with current guidelines can be used to finally provide the basis for introducing a number of bundles in the management of patients with ABP to be implemented during the following years. With this in mind, the MANCTRA-1 (coMpliAnce with evideNce-based cliniCal guidelines in the managemenT of acute biliaRy pancreAtitis) study aimed to evaluate the contemporary practice patterns of management of ABP, to compare these practices with the recommendations by the 2019 WSES guidelines for the management of severe acute pancreatitis [6], the 2018 American gastroenterological association institute guideline on initial management of acute pancreatitis [7], the 2015 Japanese guidelines for the management of acute pancreatitis [11], the 2013 International Association of Pancreatology (IAP)/American Pancreatic Association (APA) evidence-based guidelines for the management of acute pancreatitis [9] and the practice update on the management of pancreatic necrosis [22], and to demonstrate areas of sub-optimal compliance with current guidelines on ABP.

2. Methods

This is a retrospective, international, observational study developed and presented according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE, ClinicalTrials.Gov NCT04747990) [23,24]. Only patients who met the Revised Atlanta Classification (RAC) criteria [25] for a diagnosis of ABP were included in the study. Data were analysed by predetermined subgroups to allow comparison of the practice of GS, HPB, GA, and IM departments.

2.1. Endpoints and outcome measures

The primary endpoint of this study was to investigate the actual compliance with international guidelines, for which the outcome measure was the percentage of compliance with eight selected items and 14 statements that were found to be in common with the guidelines [6,7,9,11,22].

The secondary endpoints identified possible variations in the compliance stratified by the admitting speciality, and explored any statistically significant difference in the incidence of adverse events through the analysis of the mortality rate and 30-day hospital readmission due to recurrent ABP.

2.2. Ethical considerations

This study was performed under the principles of the Declaration of Helsinki and Good Epidemiological Practices, and was approved by the ethical committees of all participating centres.

2.3. Study population

All consecutive patients aged ≥16 years admitted to any of the participating general surgery (GS), hepatopancreatobiliary surgery (HPB), and/or internal medicine (IM) or gastroenterology (GA) departments with a clinical and radiological diagnosis of ABP between 01/01/2019 and 31/12/2020 were evaluated for inclusion. Patients with AP having an aetiology other than gallstones and pregnant patients were excluded.

2.4. Compliance standards

A comprehensive literature review informed the generation of potentially relevant guideline items to be analysed. Compliance was determined by comparing the collected patient data with selected recommendations from five current evidence-based guidelines [6,7,9,11,22], and was calculated by the number/percentage of patients who were managed according to each recommendation. Compliance standards were based on the following guideline domains: criteria of admission to ICU, indication and timing for contrast-enhanced CT scan, use of inflammatory and sepsis markers as prognostic factors for severe ABP and infected necrosis, role of prophylactic antibiotics (defined as the prescription of any antibiotics without a confirmed infectious aetiology, such as fever and/or elevated WBC count in the absence of a positive culture or imaging strongly suggestive of infected necrosis), nutritional support in ABP, management of the biliary tract in ABP when cholangitis and common bile duct obstruction occur, management of pancreatic necrosis, and early cholecystectomy for mild ABP.

2.5. Statistical analyses

Categorical data were reported as percentages representing the proportion of all study patients or different and well-defined cohorts, when specified, for each variable. Continuous data were expressed as mean and standard deviation. The primary analyses were descriptive assessments of surgeons' and physicians' behaviours, which were investigated based on the analysis of patients' data for unambiguous recommendations in the selected domains. Secondary analyses evaluated differences in results according to the admitting speciality. Differences between the compliance obtained in the four different subgroups were compared using the Mann-Whitney *U* test or Student's *t*-test for independent samples (for differences between more than two groups ANOVA or Kruskal-Wallis test, as appropriate, were used) for continuous data, and the Chi-square test or the Fisher's exact test, as necessary, for categorical data. All analyses were conducted under a two-tailed hypothesis. A logistic regression model was used to predict ICU admission and mortality with the examined factors. All variables that were significant at the simple regression model were included in the multiple logistic regression analysis. For all analyses, a $P < 0.05$ was considered statistically significant. The Odds Ratio (OR) or adjusted Odds Ratio (aOR) were reported with a 95% confidence interval (CI) when appropriate. Descriptive and comparative analyses were performed using R Statistical software, version 4.0.3, Stata ® 15.1 (StataCorp, College Station, Texas, USA) and the jamovi project version 2.3.2 (www.jamovi.com).

3. Results

3.1. Patient characteristics

Seventy-seven registered centres were excluded as they entered no patient data or incomplete (<95% preplanned completeness [24]) data. A total of 5320 patients were included in the database as they were admitted to any of the 150 participating GS, HPB, GA or IM departments for ABP in the study period. Complete data were available for 5275 (99.2%) patients; 4587 (87%) patients had mild ABP, 490 (9.3%) patients had moderately-severe ABP, and 198 patients had severe ABP (3.8%) according to RAC (determined within 48 h from the hospital admission).

The baseline characteristics of the study cohort, stratified according to RAC, are reported in Table 1. Data were then stratified according to the admitting speciality (Table 2); 2584 (48.9%) patients were admitted to a GS department, 304 (5.8%) to an HPB department, 1730 (32.8%) to a GA department and 657 (12.5%) to an IM department. A wide variability regarding the baseline characteristics in the different cohorts was observed in terms of age, number of previous episodes of ABP, Charlson's comorbidity index, organ failure during the hospitalization, and ICU admission.

The analysis of the risk scores, vital signs (Table 1) and the laboratory results (Supplementary Table 1) found that HPB and IM departments admitted patients with a higher clinical burden compared to GS and GA departments (Supplementary Figs. 1–3).

3.2. Clinical outcomes

Complications of ABP in the general cohort, stratified according to RAC and the admitting speciality, are reported in Supplementary Tables 2 and 3

A total of 110 (2.1%) patients in the general cohort developed gastric outlet obstruction. The highest rate of gastric outlet obstruction was reported in the HPB cohort (10 patients, 3.3%) (χ^2 9.72, $P = 0.021$; GS *vs* HPB: OR 0.68, 95%CI 0.34–1.35, $P = 0.28$ and GA *vs* IM: OR 0.45, 95%CI 0.24–0.85, $P = 0.01$). Two hundred sixty-seven (5.1%) patients in the general cohort were diagnosed with a pancreatic pseudocyst during the hospital stay, with the majority pertaining to the HPB cohort (22 patients, 7.2%) (χ^2 15.77, $P = 0.001$; GS *vs* HPB: OR 0.78, 95%CI 0.49–1.24, $P = 0.30$ and GA *vs* IM: OR 0.60, 95%CI 0.39–0.93, $P = 0.02$). Infected necrosis occurred in 243 (4.6%) patients in the general cohort, and the highest rate was reported in the HPB cohort (43 patients, 14.1%) (χ^2 111.44, $P < 0.001$; GS *vs* HPB: OR 0.27, 95%CI 0.18–0.39, $P < 0.0001$ and GA *vs* IM: OR 0.73, 95%CI 0.47–1.15, $P = 0.18$). Forty-nine (0.9%) patients in the general cohort developed an abdominal compartment syndrome. The highest rate of patients with abdominal compartment syndrome occurred in the HPB cohort (11 patients, 3.6%) (χ^2 34.15, $P < 0.001$; GS *vs* HPB: OR 0.23, 95%CI 0.11–0.49, $P = 0.0001$ and GA *vs* IM: OR 0.18, 95%CI 0.06–0.55, $P = 0.002$).

30-day hospital readmission due to recurrent ABP was reported in 250 (6.8%) patients, being highest in the GA cohort (192 patients, 11.1%) (χ^2 66.96, $P < 0.001$; GS *vs* HPB: OR 1.17, 95%CI 0.65–2.10, $P = 0.58$ and GA *vs* IM: OR 2.21, 95%CI 1.52–3.21, $P < 0.0001$) (Fig. 1).

3.3. ICU admission

Overall, 473 (9.0%) patients required ICU admission (Table 1). The highest rate of ICU admission was reported in the IM cohort (115 patients, 17.5%), followed by HPB (46 patients, 15.1%), GS (248 patients, 9.6%), and GA cohort (62 patients, 3.6%) (GS *vs* HPB: OR 0.59, 95%CI 0.42–0.83, $P = 0.002$ and GA *vs* IM: OR 0.17, 95%CI 0.12–0.24, $P < 0.0001$) (Table 2). After selecting variables associated with ICU admission with univariate logistic regression

Table 1
Baseline characteristics of the general cohort, stratified according to Revised Atlanta Classification (RAC).

Variable	Revised Atlanta Classification				
	General cohort N = 5275	Mild Acute Pancreatitis N = 4587	Moderately-severe Acute Pancreatitis N = 490	Severe Acute Pancreatitis N = 198	*P* Value
Age - Mean ± SD	63 ± 19	62 ± 19	72 ± 17	65 ± 17	<0.001
Female sex - N. (%)	2728 (52%)	2417 (53%)	223 (46%)	88 (44%)	0.001
COVID Status Positive - N. (%)	116 (2.2%)	65 (1.4%)	35 (7.1%)	16 (8.1%)	0.001
Body Mass Index (BMI) - Mean ± SD	27.3 ± 5.4	27.4 ± 5.3	26.4 ± 5.3	28.8 ± 5.7	<0.001
No previous episodes of acute pancreatitis - N. (%)	3769 (71%)	3339 (73%)	315 (64%)	115 (58%)	<0.001
Charlson's Comorbidity Index - Mean ± SD	3.37 ± 5.64	3.24 ± 5.92	4.46 ± 2.88	3.72 ± 3.52	<0.001
No history of diabetes - N. (%)	4270 (81%)	3785 (83%)	353 (72%)	132 (67%)	<0.001
History of COPD [1] - N. (%)	605 (11%)	484 (11%)	81 (17%)	40 (20%)	<0.001
History of hypertension - N. (%)	2545 (48%)	2089 (46%)	330 (67%)	126 (64%)	<0.001
History of atrial fibrillation - N. (%)	543 (10%)	407 (8.9%)	100 (20%)	36 (18%)	<0.001
History of ischaemic heart disease - N. (%)	621 (12%)	475 (10%)	114 (23%)	32 (16%)	<0.001
No history of chronic kidney disease - N. (%)	4928 (93%)	4342 (95%)	411 (84%)	175 (88%)	<0.001
History of disease of the hematopoietic system - N. (%)	176 (3.3%)	140 (3.1%)	31 (6.3%)	5 (2.5%)	<0.001
BISAP [2] score on admission					<0.001
<=3	2260 (97%)	1940 (99%)	229 (95%)	91 (72%)	
>3	73 (3.1%)	24 (1.2%)	13 (5.4%)	36 (28%)	
qSOFA score on admission - Mean ± SD	0.27 ± 0.65	0.17 ± 0.50	0.60 ± 0.90	1.12 ± 1.11	<0.001
Organ failure during the hospitalization - N. (%)					<0.001
Cardiovascular	98 (1.9%)	3 (<0.1%)	64 (13%)	31 (16%)	
Cardiovascular, Renal	32 (0.6%)	0 (0%)	23 (4.7%)	9 (4.5%)	
Cardiovascular, Respiratory	26 (0.5%)	0 (0%)	12 (2.4%)	14 (7.1%)	
Cardiovascular, Respiratory, Renal	47 (0.9%)	0 (0%)	13 (2.7%)	34 (17%)	
Renal	260 (4.9%)	16 (0.3%)	198 (40%)	46 (23%)	
Respiratory	169 (3.2%)	3 (<0.1%)	122 (25%)	44 (22%)	
Respiratory, Renal	39 (0.7%)	0 (0%)	25 (5.1%)	14 (7.1%)	
APACHE II score - Mean ± SD	6.9 ± 4.2	6.4 ± 3.8	9.5 ± 4.5	10.3 ± 5.7	<0.001
ICU admission - N. (%)	473 (9.0%)	198 (4.3%)	143 (29%)	132 (67%)	<0.001
Temperature on admission (° C) - Mean ± SD	37.57 ± 50.95	37.58 ± 54.41	37.63 ± 14.76	37.24 ± 4.65	0.996
Systolic blood pressure on admission (mmHg) - Mean ± SD	132 ± 24	132 ± 21	129 ± 30	125 ± 50	<0.001
Heart rate on admission (bpm) - Mean ± SD	81 ± 16	80 ± 15	88 ± 18	95 ± 21	<0.001
Respiratory rate on admission (breaths/min) - Mean ± SD	16.8 ± 4.0	16.5 ± 3.9	17.6 ± 4.2	19.8 ± 4.7	<0.001
SpO2% - Mean ± SD	96.81 ± 2.45	97.11 ± 2.10	95.28 ± 3.01	93.72 ± 4.21	<0.001

Results are expressed as absolute numbers (%) for categorical variables and Mean ± Standard Deviation (SD) for continuous variables; [1] **COPD**= Chronic Obstructive Pulmonary Disease; [2] **BISAP**= Bedside Index of Severity in Acute Pancreatitis.

(Supplementary Table 4), in the multivariate logistic regression analysis the admitting speciality (GS OR 108, HPB OR 940, IM OR 263), immunosuppressive medications (OR 19.0), respiratory rate (OR 1.21), blood oxygen saturation (OR 0.83), INR (OR 12.6), ALT (OR 1.00), and LDH (OR 1.00) were independent predictors of ICU admission (Supplementary Table 5).

3.4. Mortality

Overall, 178 (3.4%) patients died in the general cohort (Supplementary Table 2). The highest mortality rate was reported in the IM cohort (36 patients, 5.6%), followed by GS (93 patients, 3.6%), HPB (10 patients, 3.3%), and GA (41 patients, 2.4%) cohorts (χ^2 14.51, $P = 0.002$; GS *vs* HPB: OR 1.09, 95%CI 0.56–2.13, $P = 0.78$ and GA *vs* IM: OR 0.41, 95%CI 0.26–0.66, $P = 0.0002$).

Mortality rates were similar among the GS, HPB, GA and IM cohorts in the subgroup analyses of mild ABP ($P = 0.434$), and acute cholangitis with ($P = 0.738$) or without ($P = 0.169$) common bile duct obstruction. IM had the highest mortality rate in severe ABP (GS 34.3%, HPB 21.1%, GA 33.3%, IM 55.6%, $P = 0.043$) and infected pancreatic necrosis (GS 25.7%, HPB 11.4%, GA 18.6%, IM 38.7%, $P = 0.030$) (Fig. 2, Supplementary Table 3). Severe pancreatitis (OR 47.6), COVID + status (OR 4.92), Charlson's comorbidity index (OR 1.16), LDH (OR 1.00) and procalcitonin (OR 1.11) were independent predictors of mortality (Table 3, Supplementary Table 6).

3.5. Compliance with evidence-based guidelines for patients with acute biliary pancreatitis

Compliance with the selected evidence-based recommendations is shown in Table 4. A compliance rate of 6.1% in patients with severe ABP (GA: 11.9%, HPB 6.3%, GS 6.1%, and IM 0%; $\chi 2$ 6.71, P = 0.081; GS vs HPB: OR 1.04, 95%CI 0.12–9.20, P = 0.97 and GA vs IM: OR 10.70, 95%CI 0.57–200.70, P = 0.11) was found regarding the optimal timing for the index contrast-enhanced CT assessment. In the general cohort, 55.8% of patients underwent antibiotic prophylaxis. Antibiotics were given in 53.4% of patients with mild ABP and 83.4% with severe ABP. Patients with mild ABP received antibiotics in 59.6% of cases in the GS, 62.2% in the HPB, 38.1% in the GA, and 66.1% in the IM cohort ($\chi 2$ 221.05, P < 0.00001; GS vs HPB: OR 0.90, 95%CI 0.69–1.19, P = 0.46 and GA vs IM: OR 0.32, 95%CI 0.26–0.39, P < 0.0001).

For patients with infected pancreatic necrosis, a CT-guided fine-needle aspiration (FNA) was performed in 33.6% of patients in the general cohort. The highest compliance rate was found in the HPB cohort (56.8%) ($\chi 2$ 15.15, P = 0.001; GS vs HPB: OR 0.25, 95%CI 0.12–0.53, P = 0.0003 and GA vs IM: OR 0.72, 95%CI 0.28–1.82, P = 0.48).

Regarding early (within 24 h) oral feeding, the compliance rate with the recommendation was 44.7% in the general cohort. The highest compliance was found in the GA cohort (52.3%) ($\chi 2$ 98.14, P < 0.00001; GS vs HPB: OR 1.25, 95%CI 0.98–1.60, P = 0.07 and GA vs IM: OR 2.47, 95%CI 2.04–2.99, P < 0.00001). For patients with mild ABP, the compliance rate in the general cohort was 47.7%. The

Table 2
Baseline characteristics of the four cohorts, stratified according to admitting speciality.

Variable		Admitting speciality				
		General Surgery	HPB Surgery	Gastroenterology	Internal Medicine	*P* Value
Age - Mean ± SD		59.7 ± 18.8	61.4 ± 19.6	61.3 ± 18.5	67.3 ± 17.9	MD -14.38, 95%CI (−17.16 to −11.60), P < 0.001 MD -4.02, 95%CI (−5.94 to −2.11), P < 0.001
Female sex - N. (%)		1403 (54.3%)	155 (51.1%)	839 (48.5%)	331 (50.5%)	OR 1.14, 95%CI (0.90−1.44), P = 0.27 OR 0.92, 95%CI (0.77−1.10), P = 0.41
Body Mass Index (BMI) - Mean ± SD		27.4 ± 5.5	27.7 ± 5.8	27.0 ± 4.8	27.5 ± 5.7	MD -0.31, 95%CI (−2.27 to 1.65), P = 0.75 MD -0.005, 95%CI (−1.27 to 1.26), P = 0.99
No previous episodes of acute pancreatitis - N. (%)		1777 (68.8%)	194 (63.9%)	1342 (77.6%)	466 (71.0%)	OR 1.24, 95%CI (0.97−1.60), P = 0.07 OR 1.39, 95% CI (1.14−1.71), P = 0.001
Charlson's Comorbidity Index - Mean ± SD		3.45 ± 7.60	2.79 ± 2.41	3.34 ± 2.63	3.40 ± 2.61	MD -1.30, 95%CI (−1.72 to −0.89), P = 0.04 MD -0.28, 95%CI (−0.56 to −0.01), P = 0.46
No history of diabetes - N. (%)		2093 (81%)	237 (78%)	1392 (80.5%)	531 (80.8%)	OR 1.20, 95%CI (0.93−1.60), P = 0.20 OR 0.27, 95% CI (0.22−0.34), P < 0.0001
No history of COPD [1] - N. (%)		2338 (90.5%)	272 (89.5%)	1489 (86.1%)	552 (86.7%)	OR 1.11, 95%CI (0.75−1.65), P = 0.57 OR 1.17, 95%CI (0.91−1.50), P = 0.20
No history of hypertension - N. (%)		1423 (55.1%)	161 (53.1%)	884 (51.1%)	255 (40.1%)	OR 1.08, 95%CI (0.86−1.38), P = 0.48 OR 1.64, 95%CI (1.37−1.97), P < 0.0001
No history of atrial fibrillation - N. (%)		2348 (90.9%)	266 (87.5%)	1548 (89.5%)	551 (86.5%)	OR 1.42, 95%CI (0.98−2.04), P = 0.04 OR 1.63, 95%CI (1.26−2.11), P = 0.0002
No history of ischaemic heart disease - N. (%)		2276 (88.1%)	255 (83.9%)	1553 (89.8%)	556 (87.3%)	OR 1.42, 95%CI (1.00−1.97), P = 0.03 OR 1.59, 95%CI (1.22−2.07), P = 0.0005
No history of chronic kidney disease - N. (%)		2426 (93.9%)	282 (92.8%)	1614 (93.3%)	583 (91.5%)	OR 1.19, 95%CI (1.00−1.97), P = 0.44 OR 1.76, 95%CI (1.29−2.39), P = 0.0003
No history of disease of the hematopoietic system - N. (%)		2503 (96.9%)	291 (95.9%)	1672 (96.7%)	609 (95.6%)	OR 1.38, 95%CI (0.75−2.51), P = 0.29 OR 2.27, 95%CI (1.53−3.36), P < 0.0001
No organ failure during the hospitalization - N. (%)		2284 (88.4%)	238 (78.4%)	1524 (88.1%)	556 (84.7%)	OR 2.11, 95%CI (1.56−2.84), P < 0.0001 OR 6.01, 95%CI (4.45−7.26), P < 0.0001
ICU admission - N. (%)		248 (9.6%)	46 (15.1%)	62 (3.6%)	115 (17.5%)	OR 0.59, 95%CI (0.42−0.83), P = 0.002 OR 0.17, 95%CI (0.12−0.24), P < 0.0001
qSOFA score on admission - Mean ± SD		0.11 ± 0.6	0.85 ± 1.1	0.11 ± 0.5	0.33 ± 0.7	MD -0.90, 95%CI (−1.22 to −0.58), P < 0.001 MD -0.22, 95%CI (−0.35 to −0.09), P < 0.001
BISAP [2] score on admission - Mean ± SD		1.08 ± 1.1	1.61 ± 1.4	1.02 ± 0.9	1.39 ± 1.1	MD -0.97, 95%CI (−0.21 to −0.73), P < 0.001 MD -0.90, 95%CI (−1.07 to −0.73), P < 0.001
Glasgow-Imrie score - Mean ± SD		1.45 ± 1.2	2.50 ± 1.7	1.38 ± 1.1	1.86 ± 1.4	MD -1.97, 95%CI (−2.63 to −1.31), P < 0.001 MD -0.10, 95%CI (−0.59 to 0.38), P = 0.67
Ranson's score - Mean ± SD		1.79 ± 1.4	2.74 ± 1.7	1.68 ± 1.2	1.96 ± 1.3	MD -1.68, 95%CI (−2.27 to −1.10), P < 0.001 MD -1.12, 95%CI (−0.56 to 0.31), P = 0.56
APACHE II score - Mean ± SD		6.18 ± 4.3	6.07 ± 4.6	7.35 ± 3.2	8.97 ± 5.3	MD 1.16, 95%CI (−1.29 to 3.62), P = 0.33 MD -0.59, 95%CI (−1.94 to 0.75), P = 0.38
Temperature on admission (°C) - Mean ± SD		37.1 ± 9.3	36.8 ± 1.1	36.7 ± 2.2	36.7 ± 0.8	MD 0.45, 95%CI (−0.13 to 1.05), P = 0.12 MD -0.09, 95%CI (−0.19 to −0.01), P = 0.07
Systolic blood pressure on admission (mmHg) - Mean ± SD		127.7 ± 25.2	129.1 ± 24.4	134.1 ± 21.7	133.2 ± 23.6	MD -2.93, 95%CI (−8.15 to 2.28), P = 0.26 MD -0.92, 95%CI (−1.44 to 3.29), P = 0.44
Heart rate on admission (bpm) - Mean ± SD		84.9 ± 15.6	86.2 ± 18.3	80.2 ± 15.1	82.6 ± 16.5	MD -2.60, 95%CI (−5.42 to 0.23), P = 0.07 MD -2.10, 95%CI (−3.80 to −0.40), P = 0.01
Respiratory rate on admission (breaths/min) - Mean ± SD		18.7 ± 3.4	18.8 ± 4.5	16.9 ± 4.2	17.2 ± 3.8	MD -0.003, 95%CI (−0.67 to 0.66), P = 0.99 MD -0.78, 95%CI (−1.15 to −0.42), P < 0.001
SpO2% - Mean ± SD		96.8 ± 2.3	95.9 ± 2.9	97.2 ± 2.2	96.2 ± 3.1	MD 1.44, 95%CI (1.04−1.83), P = 0.004 MD 1.09, 95%CI (0.82−1.36), P < 0.001
Revised Atlanta Classification - N. (%)	**Mild**	2268 (87.8%)	239 (78.7%)	1520 (87.9%)	556 (84.7%)	OR 1.96, 95%CI (1.45−2.63), P < 0.0001 OR 1.31, 95%CI (1.01−1.69), P = 0.03
	Moderate	212 (8.2%)	47 (15.4%)	169 (9.8%)	66 (10.1%)	OR 0.48, 95%CI (0.34−0.68), P < 0.001 OR 0.96, 95%CI (0.71−1.30), P = 0.83
	Severe	103 (4.0%)	18 (5.9%)	41 (2.4%)	35 (5.3%)	OR 0.65, 95%CI (0.39−1.10), P = 0.11 OR 0.43, 95%CI (0.27−0.68), P = 0.0003

Results are expressed as absolute numbers (%) for categorical variables and Mean ± Standard Deviation (SD) for continuous variables; **OR**= Odds Ratio; **MD** = Mean Difference; **95%CI** = 95% Confidence Interval; [1] **COPD**= Chronic Obstructive Pulmonary Disease; [2] **BISAP**= Bedside Index for Severity in Acute Pancreatitis.

highest compliance was reported in the GA cohort (55.8%) (χ2 88.37, P < 0.00001; GS vs HPB: OR 1.06, 95%CI 0.81−1.39, P = 0.64 and GA vs IM: OR 2.51, 95%CI 2.05−3.08, P < 0.00001).

For patients with severe ABP, enteral nutrition was used in 33.2% of patients in the general cohort. The highest compliance rate was found in the HPB cohort (63.1%) (χ2 11.51, P = 0.009; GS vs HPB: OR 0.25, 95%CI 0.09−0.73, P = 0.01 and GA vs IM: OR 1.24, 95%CI 0.43−3.53, P = 0.69). For patients with infected pancreatic necrosis, the compliance rate in the general cohort was 39.3%. The highest compliance was found in the HPB cohort (61.3%), followed by the IM (38.8%), GS (37.2%) and GA (25.4%) cohorts (χ2 14.59, P = 0.002; GS vs HPB: OR 0.36, 95%CI 0.17−0.74, P = 0.005 and GA vs IM: OR 0.60, 95%CI 0.23−1.55, P = 0.29).

Regarding ERCP/ES within 72 h from hospital admission, this was performed in 46% of patients with ABP and cholangitis overall. The highest compliance rate was found in the HPB cohort (70.3%) (χ2 88.37, P < 0.00001; GS vs HPB: OR 0.21, 95%CI 0.11−0.40, P < 0.00001 and GA vs IM: OR 2.16, 95%CI 1.22−3.82, P = 0.008). ERCP/ES within 72 h was performed in 60.1% of patients with ABP and common bile duct obstruction overall. The highest compliance rate was reported in the GA cohort (80.6%) (χ2 40.26, P < 0.00001; GS vs HPB: OR 0.34, 95%CI 0.14−0.83, P = 0.02 and GA vs IM: OR

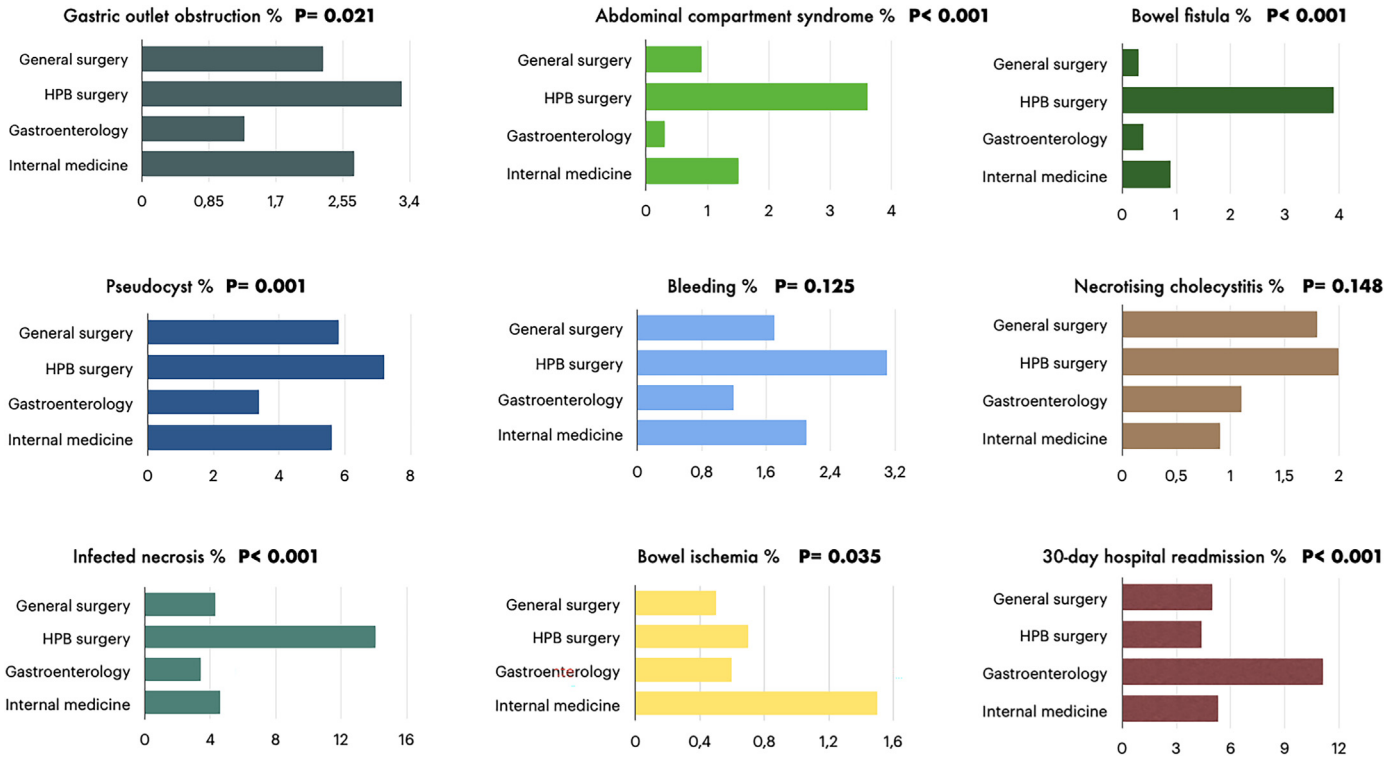

Fig. 1. Graphical representation of the clinical outcomes, stratified according to the admitting speciality.

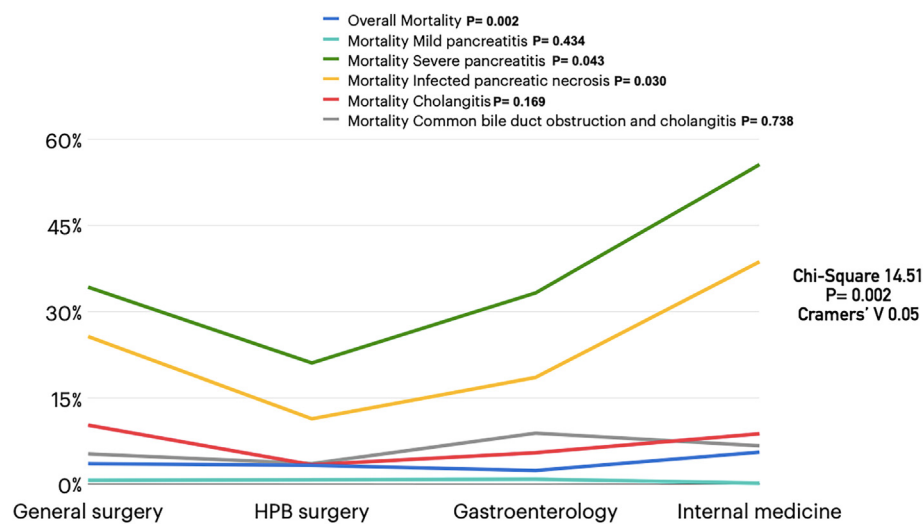

Fig. 2. Graphical representation of the mortality rates, stratified according to the admitting speciality in different subgroups (overall population, mild pancreatitis, severe pancreatitis, infected pancreatic necrosis, cholangitis, common bile duct obstruction with cholangitis).

4.12, 95%CI 1.79–9.48, P = 0.0009). In patients with ABP and common bile duct obstruction with cholangitis, this was performed in 56.7% overall. The highest compliance rate was reported in HPB (78.6%) (χ2 8.46, P = 0.037; GS vs HPB: OR 0.24, 95%CI 0.09–0.65, P = 0.005 and GA vs IM: OR 5.00, 95%CI 1.99–12.57, P = 0.0006).

For patients with infected pancreatic necrosis, percutaneous or endoscopic drainage as the first-line treatment was adopted in 33.7% of the patients. The highest level of compliance was reported in the HPB cohort (39.5%) (χ2 6.33, P = 0.096; GS vs HPB: OR 0.42, 95%CI 0.20–0.89, P = 0.02 and GA vs IM: OR 0.72, 95%CI 0.28–1.82, P = 0.84).

Patients with mild ABP underwent laparoscopic cholecystectomy during index admission in 29% of the cases in the general cohort. The highest level of compliance was reported in the GS cohort (39.8%) (χ2 354.64, P < 0.00001; GS vs HPB: OR 1.51, 95%CI 1.13–2.01, P = 0.005 and GA vs IM: OR 0.28, 95%CI 0.22–0.35, P < 0.00001).

Funnel plots in Fig. 3 display the proportion of compliance (in percentage) to the four most evidence-based guidelines items in the respective cohorts by each participating centre. Fig. 3A shows that, in the case of antibiotic prophylaxis, as the patients' number increases, the compliance rates tend to be significantly higher. No outlier, instead, emerged in the case of the compliance to early oral/

Table 3
Multiple logistic regression model, outcome Mortality.

Variable	Odds Ratio(OR)	95% Confidence Interval (CI)	*P*-value
Revised Atlanta Classification			
Mild acute pancreatitis	–	–	
Moderately severe acute pancreatitis	8.45	0.33–164	0.195
Severe acute pancreatitis	47.6	1.52–1.387	0.031
Age	0.98	0.94–1.02	0.384
COVID Status			
Negative	–	–	
Positive	4.92	1.17–22.6	0.032
Untested	2.19	0.52–9.41	0.282
Previous episodes of pancreatitis			
No	–	–	
Not known	3.33	0.18–33.5	0.347
Yes	0.79	0.22–2.71	0.713
Charlson's comorbidity index	1.16	1.04–1.28	0.004
Clinical history of diabetes			
Diabetes with organ dysfunction	–	–	
Diabetes without organ dysfunction	0.32	0.05–2.14	0.237
No	0.20	0.03–1.22	0.075
Clinical history of chronic pulmonary disease			
No	–	–	
Yes	1.25	0.34–4.28	0.725
Clinical history of hypertension			
No	–	–	
Yes	1.13	0.30–4.59	0.855
Clinical history of atrial fibrillation			
No	–	–	
Yes	0.61	0.08–3.43	0.604
Clinical history of ischaemic heart disease			
No	–	–	
Yes	2.57	0.64–10.3	0.176
Organ failure during the hospital stay[a]			
No	–	–	
Yes	0.60	0.03–16.8	0.756
Systolic blood pressure	0.98	0.95–1.00	0.114
Heart rate on admission	1.01	0.97–1.05	0.582
Respiratory rate on admission	1.05	0.95–1.13	0.204
Blood oxygen saturation on admission	0.94	0.82–1.07	0.324
WBC on admission	0.58	0.32–0.96	0.059
Neutrophils on admission	1.65	1.00–2.97	0.076
INR on admission	0.48	0.07–2.28	0.397
C-Reactive Protein on admission	1.00	0.99–1.01	0.707
LactateDeHydrogenase on admission	1.00	1.00–1.00	0.043
Procalcitonin on admission	1.11	1.01–1.21	0.016
Lactate on admission	1.46	0.98–2.17	0.059
Cholangitis			
No	–	–	
Yes	0.86	0.18–3.58	0.847
Infected necrosis			
No	–	–	
Yes	4.05	0.96–16.9	0.052
Abdominal compartment syndrome			
No	–	–	
Yes	2.79	0.35–23.1	0.329
Necrotising cholecystitis			
No	–	–	
Yes	4.24	0.56–28.5	0.144

+The following variables have been excluded from the model due to multicollinearity issues: Admitting Speciality, Gastric outlet obstruction, Pseudocyst, Timing of surgical necrosectomy, Bleeding, Bowel ischaemia, Bowel fistula, Antibiotic prophylaxis, Antifungal prophylaxis, Use of somatostatin analogs.

[a] This variable has been recoded to two categories.

enteral feeding (Fig. 3B) and the compliance to the step-up approach (Fig. 3D) respectively in the cohorts of patients with severe ABP and infected necrosis, where the compliance does not significantly differ according to the patients' number. Conversely, concerning the compliance to laparoscopic cholecystectomy at index admission (Fig. 3C), we observed many outliers with an unusually low compliance to the guidelines as the patients' number is greater than 100, while in the same patients' range there was no outlier with an opposite tendency (i.e. significantly higher compliance).

Table 4
Compliance with the selected evidence-based recommendations.

Statement		Admitting speciality					
	Target population	General cohort	General Surgery	HPB Surgery	Gastroenterology	Internal Medicine	*P* Value
Patients with organ failure should be admitted to an intensive care unit (ICU)[a]	Patients with severe acute biliary pancreatitis	133 (66.8%)	70 (66.7%)	13 (73.7%)	22 (52.4%)	28 (77.8%)	$P = 0.101$ OR 0.79, 95%CI (0.26−2.40), P = 0.68 OR 0.29, 95%CI (0.10−0.81), P = 0.02
All patients with severe acute pancreatitis need to be assessed with CE-CT [b]	Patients with severe acute biliary pancreatitis	142 (71.9%)	77 (73.3%)	13 (73.7%)	26 (64.3%)	26 (77.8%)	$P = 0.651$ OR 1.10, 95%CI (0.36−3.36), P = 0.87 OR 0.60, 95%CI (0.22−1.61), P = 0.31
Optimal timing for the index CE-CT assessment is 72–96 h after onset of symptoms [b]	Patients with severe acute biliary pancreatitis	12 (6.1%)	6 (5.7%)	1 (6.3%)	5 (11.9%)	0 (0%)	$P = 0.081$ OR 1.04, 95%CI (0.12−9.20), P = 0.97 OR 10.70, 95% CI (0.57 −200.70), P = 0.11
C-reactive protein (CRP) level ≥ 150 mg/l at third day can be used as a prognostic factor for severe acute pancreatitis ◦	All patients with acute biliary pancreatitis	4055 (76.8%)	1994 (77.2%)	250 (82.2%)	1194 (69.1%)	617 (94.1%)	$P < 0.00001$ OR 0.73, 95%CI (0.54−0.99), P = 0.04 OR 0.14, 95%CI (0.10−0.20), P < 0.00001
Routine prophylactic antibiotics are not recommended for all patients with acute pancreatitis	1. All patients with acute biliary pancreatitis under antibiotics	2943 (55.8%)	1611 (62.3%)	203 (66.6%)	677 (39.1%)	452 (68.8%)	$P < 0.00001$ OR 0.82, 95%CI (0.84−1.06), P = 0.13 OR 0.29, 95%CI (0.24−0.35), P < 0.00001
	2. Patients with mild acute biliary pancreatitis under antibiotics	2450 (53.4%)	1353 (59.6%)	149 (62.2%)	580 (38.1%)	368 (66.1%)	$P < 0.00001$ OR 0.90, 95%CI (0.69−1.19), P = 0.46 OR 0.32, 95%CI (0.26−0.39), P < 0.00001
	3. Patients with severe acute biliary pancreatitis under antibiotics	165 (83.4%)	89 (84.8%)	15 (78.9%)	31 (73.8%)	30 (86.1%)	$P = 0.668$ OR 1.19, 95% (0.31−4.60), P = 0.80 OR 0.52, 95% (0.16−1.69), P = 0.27
	4. Patients with infected pancreatic necrosis under antibiotics	207 (85.2%)	99 (87.6%)	41 (93.2%)	45 (76.3%)	22 (74.2%)	$P = 0.015$ OR 0.37, 95%CI (0.08−1.72), P = 0.21 OR 1.26, 95%CI (0.45−3.48), P = 0.66
Serum measurements of procalcitonin (PCT) may be valuable in predicting the risk of developing infected pancreatic necrosis [a]	1. Patients with severe acute biliary pancreatitis	61 (30.8%)	37 (35.6%)	4 (22.2%)	6 (14.6%)	14 (38.9%)	$P = 0.701$ OR 1.93, 95%CI (0.59−6.30), P = 0.27 OR 0.26, 95%CI (0.09−0.77), P = 0.02
	2. Patients with infected pancreatic necrosis	72 (29.6%)	48 (42.8%)	7 (18.2%)	9 (15.5%)	8 (26.7%)	$P = 0.874$ OR 3.86, 95%CI (1.58−9.41), P = 0.003 OR 0.51, 95%CI (0.17−1.48), P = 0.21

(*continued on next page*)

Table 4 (*continued*)

Statement		Admitting speciality					
	Target population	General cohort	General Surgery	HPB Surgery	Gastroenterology	Internal Medicine	*P* Value
A CT-guided fine-needle aspiration (FNA) for Gram stain and culture can confirm an infected severe acute pancreatitis and drive antibiotic therapy [b]	Patients with infected pancreatic necrosis	82 (33.6%)	29 (25.7%)	25 (56.8%)	17 (28.8%)	11 (35.5%)	$P = 0.001$ OR 0.25, 95%CI (0.12−0.53), P = 0.0003 OR 0.72, 95%CI (0.28−1.82), P = 0.48
Early (within 24 h) oral feeding as tolerated, rather than keeping the patient nil per os, is recommended in patients with acute pancreatitis	1. All patients with acute biliary pancreatitis	2358 (44.7%)	1136 (44.0%)	117 (38.7%)	904 (52.3%)	201 (30.5%)	$P < 0.00001$ OR 1.25, 95%CI (0.98−1.60), P = 0.07 OR 2.47, 95%CI (2.04−2.99), P < 0.00001
	2. Patients with mild acute biliary pancreatitis	2188 (47.7%)	1047 (46.2%)	107 (44.8%)	848 (55.8%)	186 (33.5%)	$P < 0.00001$ OR 1.06, 95%CI (0.81−1.39), P = 0.64 OR 2.51, 95%CI (2.05−3.08), P < 0.00001
Enteral nutrition is recommended to prevent gut failure and infectious complications in patients with acute pancreatitis and inability to feed orally.	1. Patients with severe acute biliary pancreatitis	66 (33.2%)	35 (33.3%)	12 (63.1%)	11 (28.6%)	8 (19.5%)	$P = 0.009$ OR 0.25, 95%CI (0.09−0.73), P = 0.01 OR 1.24, 95%CI (0.43−3.53), P = 0.69
	2. Patients with infected pancreatic necrosis	95 (39.3%)	42 (37.2%)	27 (61.3%)	15 (25.4%)	11 (38.8%)	$P = 0.002$ OR 0.36, 95%CI (0.17−0.74), P = 0.005 OR 0.60, 95%CI (0.23−1.55), P = 0.29
Total parental nutrition (TPN) should be avoided, but partial parental nutrition integration should be considered to reach caloric and protein requirements if enteral rout is not completely tolerated. [c]	1. Patients with severe acute biliary pancreatitis on TPN	71 (36.2%)	37 (34.3%)	4 (21.1%)	12 (31.0%)	18 (52.8%)	$P = 0.717$ OR 1.93, 95%CI (0.59−6.30), P = 0.27 OR 0.39, 95%CI (0.15−1.00), P = 0.05
	2. Patients with infected pancreatic necrosis on TPN	83 (34.4%)	39 (34.5%)	11 (27.3%)	21 (35.6%)	12 (38.7%)	$P = 0.940$ OR 1.55, 95%CI (0.71−3.42), P = 0.27 OR 0.85, 95%CI (0.34−2.11), P = 0.73
Early ERCP/ES should be performed in gallstone-induced acute pancreatitis when complications of cholangitis and common bile duct obstruction occur [d]	1. Patients with acute biliary pancreatitis and cholangitis (ERCP/ES performed within 72h)	251 (46.0%)	74 (33.4%)	40 (70.3%)	112 (56.5%)	25 (38.2%)	$P < 0.00001$ OR 0.21, 95%CI (0.11−0.40), P < 0.00001 OR 2.16, 95%CI (1.22−3.82), P = 0.008
	2. Patients with acute biliary pancreatitis and CBD obstruction (ERCP/ES performed within 72h)	248 (60.1%)	107 (48.0%)	19 (74.1%)	107 (80.6%)	15 (51.6%)	$P < 0.00001$ OR 0.34, 95%CI (0.14−0.83), P = 0.02 OR 4.12, 95%CI (1.79−9.48), P = 0.0009
	3. Patients with acute biliary pancreatitis and CBD obstruction and cholangitis (ERCP/ES performed within 72h)	118 (56.7%)	34 (46.0%)	21 (78.6%)	54 (69.6%)	9 (33.3%)	$P = 0.037$ OR 0.24, 95%CI (0.09−0.65), P = 0.005 OR 5.00, 95%CI (1.99−12.57), P = 0.0006
In infected pancreatic necrosis, percutaneous or endoscopic drainage as the first line treatment (step-up approach) delays the surgical treatment to a more	Patients with infected pancreatic necrosis	83 (33.7%)	24 (21.4%)	17 (39.5%)	17 (29.3%)	11 (36.6%)	$P = 0.096$ OR 0.42, 95%CI (0.20−0.89),

Table 4 (*continued*)

Statement	Target population	Admitting speciality					
		General cohort	General Surgery	HPB Surgery	Gastroenterology	Internal Medicine	*P* Value
favourable time or even results in complete resolution of infection in 25–60% of patients and it is recommended as the first line of treatment							P = 0.02 OR 0.72, 95%CI (0.28–1.82), P = 0.84
Therapeutic intervention for infected pancreatic necrosis should be performed after 4 weeks of onset, when the necrosis has been sufficiently walled off	Patients with infected pancreatic necrosis	29 (37.2%)	9 (27.9%)	11 (68.4%)	7 (31.8%)	2 (23.1%)	P = 0.018 OR 0.25, 95%CI (0.10–0.67), P = 0.005 OR 1.92, 95%CI (0.37–9.88), P = 0.43
Laparoscopic cholecystectomy during index admission, rather than after discharge, is recommended in mild acute gallstones pancreatitis	Patients with mild acute biliary pancreatitis	1328 (29%)	902 (39.8%)	72 (30.3%)	176 (11.6%)	178 (32.3%)	P < 0.00001 OR 1.51, 95%CI (1.13–2.01), P = 0.005 OR 0.28, 95%CI (0.22–0.35), P < 0.00001

* Intensive Care Unit; [§] Contrast-enhanced computed tomography; ◦ C-reactive Protein; [c] Bedside Index of Severity of Acute Pancreatitis and Acute Physiology and Chronic Health Evaluation II; [a] Procalcitonin; [b] Fine-needle aspiration; [c] Total Parental Nutrition; [d] Endoscopic Retrograde CholangioPancreatography/Endoscopic Sphincterotomy

4. Discussion

Publication of nationally or internationally developed and approved guidelines alone is insufficient to modify the practice of non-specialists and raises the question of how best to spread guideline recommendations [2,12–17]. We showed that there is still a lack of compliance to practice guidelines, especially in terms of optimal timing for the index CT scan, the use of prophylactic antibiotics, nutritional support, and implementation of early cholecystectomy strategies to minimise the incidence of further episodes of ABP. Moreover, we have highlighted several substantial differences in practice patterns between general surgeons, HPB surgeons, gastroenterologists and internal medicine physicians that may have impacted the outcomes of patients with ABP. Different baseline characteristics of the patients admitted to each department may have contributed to the outcomes, especially in terms of ICU admission and mortality. However, regarding the compliance to the most agreed items of the guidelines, such as the use of prophylactic antibiotics, enteral nutrition, or index cholecystectomy, we cannot ignore that the compliance level varied according to the admitting speciality. Moreover, as demonstrated by the analysis of risk factors for adverse outcomes, the admitting speciality was an independent predictor of ICU admission in the multivariate logistic regression analysis. The admitting speciality was also a predictor of mortality in the univariate analysis, though it lost statistical significance in the multivariate analysis. Many factors may contribute to the high variability in the compliance rate for each selected item. These factors include hospital facilities, organisational pathways, and surgeons' skills in laparoscopic surgery for hot gallbladders. In our study, patient populations on which each item was assessed have been made as homogeneous as possible to limit the influence of confounding factors. So, it seems unlikely that substantial differences in practice patterns between general surgeons, HPB surgeons, gastroenterologists and internal medicine physicians are to be searched in factors other than the confidence in applying the guidelines in everyday clinical practice and suboptimal organisational pathways.

Compliance was satisfactory for some items, including the indication to perform a CT scan in patients with severe ABP, even if the compliance turned out to be very low when we looked into the timing for performing the index CT scan. Our study found that only 6.1% of the patients in the general cohort underwent CT scan 72–96 h after onset of symptoms, whereas 28% of the patients were CT scanned on hospital admission. According to Spanier et al., although CT scan is frequently acquired early in the course of AP in everyday practice, its yield has shown to be low and has no implications in clinical management [26].

Although it is commonly believed that non-compliance with published guidelines indicates areas in which consensus recommendations are based on insufficient evidence [14], the results of our study demonstrated lack of compliance in areas where randomised controlled trials have already resolved controversial issues during the last ten years. Prophylactic antibiotics were frequently prescribed, with almost 50% of patients in the general cohort and 47% of those in the mild ABP cohort receiving prophylactic antibiotics on admission. From the global healthcare perspective, inappropriate use of antibiotics is a key driver in antibiotic resistance, which has risen alarmingly over the last 30 years, and represents a potent threat to the welfare of humanity in the 21st century [27]. More debated is the role of prophylactic antibiotics for patients with infected necrosis [28,29]. Several randomised controlled trials and subsequent meta-analyses failed to demonstrate reduced infection rates of pancreatic necrosis through the prophylactic use of antibiotics [30–33]. 83.4% of the patients in the severe ABP cohort received antibiotic prophylaxis without any proof of infection, with a range between 86.1% in the IM cohort and 73.8% in the GA cohort, in keeping with previous national studies [15,16]. Overuse was also seen in mild cases, with 47% of patients with mild ABP receiving antibiotics in our study, compared to 44% in the study by Barrie et al. [16] and 48% in the study by Talukdar et al. [34]. Regarding the type of nutritional support implemented in the early stages of ABP, we found a significant discordance with the current guideline recommendations [35]. Early re-initiation of oral nutrition with a non-liquid diet is recommended for mild ABP [7,9], with some variability concerning refeed timing and type of diet [10,11,36]. In our study, early oral feeding was implemented for only 44.7% of patients in the general cohort and 47.7% of patients in the mild ABP cohort, with wide variability across the different admitting specialities. In the study by Machicado et al. [37], only 27% of clinicians adhered to early oral nutrition within 24 h, and 41% kept patients with mild ABP nil per os for over 48 h, whereas, in the study by Masamune et al. [38], enteral nutrition was given in 31.8%

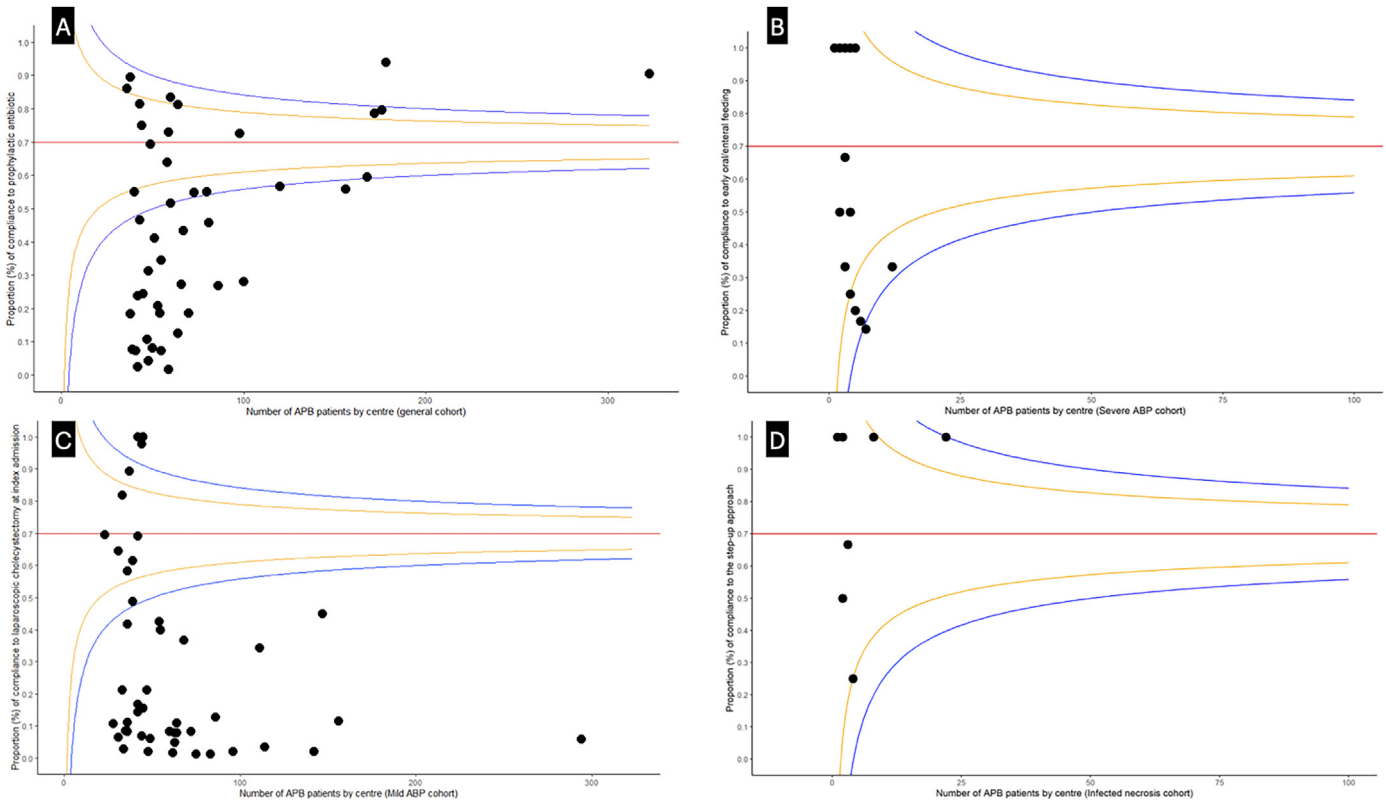

Fig. 3. Funnel plots with confidence bands displaying the percentage of compliance to four guidelines items by the total number of patients per each centre. Reference for compliance has been set to 70%. Orange and blue lines represent respectively 95% and 99.8% confidence limits. A) Compliance to the guidelines on antibiotic prophylaxis in the general cohort (only centres with a patients' number n > 30 were considered). B) Compliance to the administration of early oral feeding in the cohort of patients with severe ABP (only centres with a patients' number n > 30 were considered). C) Compliance to the laparoscopic cholecystectomy during index admission in the cohort of patients with mild ABP (only centres with a patients' number n > 30 were considered). D) Compliance to the step-up approach in the cohort of patients with infected necrosis (only centres with a patients' number n > 5 were considered).

of severe cases, but majority cases received it after 48 h. Only 33.2% of patients in the severe ABP cohort and 39.3% of patients with infected pancreatic necrosis received enteral feeding on admission, compared to 21% of patients with severe ABP who received enteral feeding in the study by Tan et al. [36]. Potential explanations for practice variation may include personal beliefs regarding the duration of "pancreas rest", caution for exacerbating pain and other symptoms, or, more probably, lack of awareness of current evidence. Other factors that might play a role include the diversity of hospital protocols, delayed translation of evidence into medical care, or reluctance of surgeons and physicians to comply with guidelines [37].

In patients with ABP, a Cochrane meta-analysis supported the use of ERCP in patients with cholangitis and/or common bile duct obstruction [39], whereas, in patients with no cholangitis, the American Gastroenterological Association suggests against the routine use of urgent ERCP [6,7,11]. In our study, only 46% of patients with ABP and acute cholangitis underwent ERCP and sphincterotomy within 72 h of admission, whereas 60.1% of patients with ABP and common bile duct obstruction did.

Approximately 10–20% of patients with AP develop pancreatic necrosis [25], and about one-third of them develop infection of the necrotic tissue [40]. While sterile necrosis is associated with 5%–10% of mortality, the mortality rate increases to 20%–30% when infection occurs [40–45]. Patients with infected pancreatic necrosis may require radiologic or endoscopic or surgical intervention in up to 40% of cases [40]. The step-up approach, consisting of percutaneous catheter drainage, followed, if necessary, by minimally invasive necrosectomy, has replaced open surgery as the standard of care [40,46]. More recently, an endoscopic approach has been demonstrated to be a less invasive technique [47,48] which can also be performed in a step-up fashion, starting with endoscopic transluminal drainage, and followed by endoscopic necrosectomy if the drainage does not result in clinical improvement [49]. In our study, only 33.7% of patients with infected pancreatic necrosis underwent a step-up approach as their first treatment, rather than upfront surgery, and only 37.2% of them underwent treatment after four weeks of symptom onset, as recommended by guidelines.

Only 29% of the patients with mild ABP underwent cholecystectomy on the same hospital admission, with wide variation between admitting specialities. The highest compliance rate was reported in the GS cohort (39.8% vs 32.3%, 30.3%, and 11.6% in IM, HPB and GA cohorts). Compared to delayed laparoscopic cholecystectomy, early laparoscopic cholecystectomy for mild stages during the index admission, is equally safe and feasible and significantly reduces the recurrence rate of ABP [20,50–52]. Well-designed studies also have demonstrated that many episodes of recurrent ABP occur before an interval cholecystectomy can be performed, making index admission cholecystectomy the ideal strategy to reduce morbidity and minimise overall healthcare costs [53,54]. Notably, in our study, 30-day hospital readmission rates were higher in GA departments, where laparoscopic cholecystectomy during index admission was performed less frequently than in GS and HPB cohorts. Our study also revealed that 6.6% of patients in the general cohort and 6.3% of those in the mild ABP cohort were readmitted with a recurrence while awaiting interval cholecystectomy, with other studies reporting rates of up to 20% [53,55]. In contrast to the study by Green et al. [56], where patients were more

likely to receive early definitive treatment if they were treated in regional specialist HPB centres, in our study patients admitted to GS departments with mild ABP had a higher chance to undergo an index admission cholecystectomy compared to those admitted to HPB ones, with the likely explanation being a lack of theatre slots for benign diseases in high specialised HPB departments. We also observed that, regarding laparoscopic cholecystectomy at index admission, there was an unusually low compliance to the guidelines as the number of patients admitted at each centre increased over 100.

Previous studies compared the management of ABP and adherence to guidelines among academic surgical services, HPB services, academic medicine, and non-academic medicine in the same institution and showed that adherence to guidelines for the management of AP is inadequate, and non-uniformity exists across different services within the same institution [57]. The study by Aly et al. [58] showed differences between the reported practice of HPB surgeons and non-specialists in the management of ABP, suggesting that the specialists may be more aware of the guidelines and the evidence supporting them. In our study, the analysis of the level of compliance with items related to the treatment of more complex ABP cases (e.g. severe or with necrosis) showed that patients admitted to HPB departments were treated in line with the recommendations of the guidelines more commonly than those admitted to the other specialities.

According to Connor et al. [59], for evidence-based guidelines to be effective, feedback to surgeons and physicians who deal with AP is necessary. The authors found that by comparing outcomes pre- and post-audit feedback performed nine months after the implementation of guidelines, there was a significant increase in the number of patients who underwent definitive treatment for mild ABP. Post-audit feedback showed a significant reduction in the number of CT scans performed for patients with mild AP, and mortality also decreased. Implementation strategies based on surgical audits, which involve the systematic, critical analysis of the quality of care for patients with ABP, can facilitate the goal of improving compliance to guidelines.

4.1. Study limitations

There are several limitations to this study. It is a retrospective study performed by chart review; therefore, we could not adequately account for the rationale that each centre may have used to manage included patients. Although instructions on how to fill the study eCRF were provided over the whole duration of the study period via personal emails, websites and ad-hoc tutorials, the retrospective study design may have exposed the risk of recall bias. Regarding the choice of early cholecystectomy for mild cases, it must be accepted that there may well be a cohort of patients that were not suitable to be treated as per guidelines which may have affected the given results. The guidelines are variable in quality, which may influence compliance. In 2010, Loveday et al. [60] reviewed the quality of 30 guidelines on AP published from 1985 to 2010. The authors found that the quality of the guidelines did not improve over time. The guidelines endorsed by a professional body had higher scores than those without official endorsement. Although, due to obvious chronological reasons, the 2019 WSES guidelines, the 2018 American gastroenterological association institute guidelines, the 2015 Japanese guidelines, the 2013 IAP/APA evidence-based guidelines, and the 2020 AGA practice update on the management of pancreatic necrosis guidelines were not evaluated in this systematic review, the previously published version of the Japanese guidelines [61]were selected as one of the four most up-to-date guidelines with high-quality scores. The 2013 IAP/APA guidelines have also reached high-quality scores in our evaluation performed with the AGREE II (Appraisal of Guidelines for Research & Evaluation) instrument. Another criticism of our study could be the higher representation of European countries compared to other continents [24], as it can be argued that the responses could be skewed due to higher representation from one continent and results may not be generalisable.

In 2020, the COVID-19 pandemic profoundly impacted the medical community. The constant increase in the number of patients requiring treatment became a massive challenge for the healthcare systems of many involved countries. The outbreak of the COVID-19 pandemic could have influenced in many ways the daily clinical practice for patients with ABP, leading to a failure in adherence to the recommendations provided by the guidelines, especially those regarding the early and definitive treatment with cholecystectomy or ERCP and ES. As we argue that, during the COVID-19 pandemic, the tendency to disregard the guidelines recommendations has been more marked than usual, we planned a sub-analysis of the MANCTRA-1 study [24], and we will try to find out if the care of ABP patients during the COVID-19 pandemic resulted in a higher rate of adverse outcomes compared to non-pandemic times due to the lack of compliance to guidelines. However, some signs of the impact of the COVID-19 pandemic on ABP patients' outcomes have already been reported in the present paper, where COVID + status was an independent predictor of mortality, in keeping with the results of the COVID PAN collaborative study [63], that showed patients with AP and coexistent SARS-CoV-2 infection are at increased risk of severe AP, worse clinical outcomes, prolonged length of hospital stay and high 30-day mortality.

The short delay between the actual date of publication of the recommendations and the study inclusion period may represent another limiting factor. Research suggests that, on average, it takes up to 17 years for only 14% of published evidence to translate into practice [62]. Currently, implementation strategies which include the measurement acceptability, appropriateness, costs, and sustainability of the evidence-based intervention, seem to be among the most reliable strategies for implementing research into practice. More recently, scientists who work in the field of knowledge translation reported that to close the gap between research and practice, research findings must be made more accessible to policymakers, professional societies and practitioners, as well as pushing these parties to adopt more timely evidence-based practices. With this in mind, the results of the MANCTRA-1 study will be analysed to provide the basis for introducing a number of bundles in ABP patients' management to be disseminated during the following years. Following the introduction of the ABP bundles in 2023, the MANCTRA-2 prospective international study will be launched in 2025 to assess the potential advancements for ABP patients' care in those centres that have taken part in the project.

5. Conclusions

The results of this study showed an overall poor compliance with evidence-based guidelines in the management of ABP, with wide variability based on the admitting speciality. The most commonly discordant gaps between daily clinical practice and recommendations included the optimal timing for the index CT scan, the use of prophylactic antibiotics, nutritional support, and the implementation of early cholecystectomy strategies to minimise the rate of hospital readmission and further episodes of ABP.

Contributions of authors

Mauro Podda: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acted as study principal investigator and guarantor of the integrity and precision of the manuscript with

the other co-authors as well as be informed of other authors' roles in the work; Acquisition, analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Daniela Pacella: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acted as statistical advisor and data management lead; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Gianluca Pellino: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Federico Coccolini: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acquisition, Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Alessio Giordano: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acquisition, Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Salomone Di Saverio: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Francesco Pata: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Benedetto Ielpo: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acquisition, Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Francesco Virdis: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acquisition, Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Dimitrios Damaskos: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Belinda De Simone: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acquisition, Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Ferdinando Agresta: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acquisition, Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Massimo Sartelli: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Ari Leppaniemi: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Cristiana Riboni: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acquisition, Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Vanni Agnoletti: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Damian Mole: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published.Yoram Kluger: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Fausto Catena: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. Adolfo Pisanu: Conception and design of the MANCTRA project and the MANCTRA-1 study; Analysis, and interpretation of data for the study; Drafting the study and revising it critically for important intellectual content; Final approval of the version to be published. The MANCTRA-1 Collaborative Group: Conception and design of the MANCTRA project and the MANCTRA-1 study; Acquisition of data for the study; Revising it critically for important intellectual content; Final approval of the version to be published.

Funding

This research has not received any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

The study meets and conforms to the standards outlined in the principles of the Declaration of Helsinki of 1975 (as revised in 2008) and in accordance with 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. PG/2021/7108). All the investigators conducted the study according to the rules of the ethics committee regarding the retrospective collection of data.

Availability of data and other materials

The data that support the findings of this study will be available upon request from the principal investigator [MP].

Declaration of competing interest

The authors report no conflict of interest.

Acknowledgements

This study has been endorsed by: The World Society of Emergency Surgery (WSES), the Italian Society of Endoscopic Surgery and New Technologies (SICE), the Association of Italian Surgeons in Europe (ACIE), the Italian Surgical Research Group (ItSurg), the American College of Surgeons (ACS) - Italy Chapter, and the Association of Spanish Surgeons - HPB Section (AEC).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2022.07.007.

References

[1] Roberts SE, Morrison-Rees S, John A, et al. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology 2017;17:155–65.
[2] Andersson B, Appelgren B, Sjödin V, et al. Acute pancreatitis–costs for healthcare and loss of production. Scand J Gastroenterol 2013;48:1459–65.
[3] Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology 2015;149:1731–41.
[4] Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. N Engl J Med 2016;375:1972–81.
[5] Kandasami P, Harunarashid H, Kaur H. Acute pancreatitis in a multi-ethnic population. Singap Med J 2002;43:284–8.
[6] Leppäniemi A, Tolonen M, Tarasconi A, et al. WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg 2019;14:27. https://doi.org/10.1186/s13017-019-0247-0. 2019.
[7] Crockett SD, Wani S, Gardner TB, et al. American gastroenterological association institute guideline on initial management of acute pancreatitis. Gastroenterology 2018;154:1096–101.
[8] Working party of the British society of gastroenterology; association of surgeons of great britain and Ireland; pancreatic society of great britain and Ireland; association of upper GI surgeons of great britain and Ireland. UK guidelines for the management of acute pancreatitis. Gut 2005;54(Suppl 3):iii1–9. https://doi.org/10.1136/gut.2004.057026. Suppl 3.
[9] Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13(4 Suppl 2):e1–15. https://doi.org/10.1016/j.pan.2013.07.063.
[10] Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400–15.
[11] Yokoe M, Takada T, Mayumi T, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci 2015;22:405–32.
[12] Toh SK, Phillips S, Johnson CD. A prospective audit against national standards of the presentation and management of acute pancreatitis in the South of England. Gut 2000;46:239–43.
[13] Gurusamy KS, Farouk M, Tweedie JH. UK guidelines for management of acute pancreatitis: is it time to change? Gut 2005;54:1344–5.
[14] Lankisch PG, Weber-Dany B, Lerch MM. Clinical perspectives in pancreatology: compliance with acute pancreatitis guidelines in Germany. Pancreatology 2005;5:591–3.
[15] Baltatzis M, Jegatheeswaran S, O'Reilly DA, et al. Antibiotic use in acute pancreatitis: global overview of compliance with international guidelines. Pancreatology 2016;16:189–93.
[16] Barrie J, Jamdar S, Smith N, et al. Mis-use of antibiotics in acute pancreatitis: insights from the United Kingdom's National Confidential Enquiry into patient outcome and death (NCEPOD) survey of acute pancreatitis. Pancreatology 2018;18:721–6.
[17] Talukdar R, Tsuji Y, Jagtap N, et al. Non-compliance to practice guidelines still exist in the early management of acute pancreatitis: time for reappraisal? Pancreatology 2021;S1424–3903(21). https://doi.org/10.1016/j.pan.2021.05.301. 00471-00473.
[18] Andersson R. Compliance with guidelines for the management of acute pancreatitis: a protocol is not enough. Scand J Gastroenterol 2008;43:515–7.
[19] Mueck KM, Wei S, Pedroza C, et al. Gallstone pancreatitis: admission versus normal cholecystectomy-a randomized trial (gallstone PANC trial). Ann Surg 2019;270:519–27.
[20] Riquelme F, Marinkovic B, Salazar M, et al. Early laparoscopic cholecystectomy reduces hospital stay in mild gallstone pancreatitis. A randomized controlled trial. HPB (Oxford) 2020;22:26–33.
[21] Isbell KD, Wei S, Dodwad SM, et al. Impact of early cholecystectomy on the cost of treating mild gallstone pancreatitis: gallstone PANC trial. J Am Coll Surg 2021;233:517–25.
[22] Baron TH, DiMaio CJ, Wang AY, et al. American gastroenterological association clinical practice update: management of pancreatic necrosis. Gastroenterology 2020;158:67–75.
[23] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.
[24] Podda M, Pellino G, Coccolini F, et al. Compliance with evidence-based clinical guidelines in the management of acute biliary pancreatitis: the MANCTRA-1 study protocol. Updates Surg 2021;73:1757–65.
[25] Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
[26] Spanier BW, Nio Y, van der Hulst RW, et al. Practice and yield of early CT scan in acute pancreatitis: a Dutch Observational Multicenter Study. Pancreatology 2010;10:222–8.
[27] Arias CA, Murray BE. Antibiotic-resistant bugs in the 21st century–a clinical super-challenge. N Engl J Med 2009;360:439–43.
[28] Lim CL, Lee W, Liew YX, et al. Role of antibiotic prophylaxis in necrotizing pancreatitis: a meta-analysis. J Gastrointest Surg 2015;19:480–91.
[29] Ukai T, Shikata S, Inoue M, et al. Early prophylactic antibiotics administration for acute necrotizing pancreatitis: a meta-analysis of randomized controlled trials. J Hepatobiliary Pancreat Sci 2015;22:316–21.
[30] Isenmann R, Rünzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004;126:997–1004.
[31] Dellinger EP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg 2007;245:674–83.
[32] Bai Y, Gao J, Zou DW, et al. Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials. Am J Gastroenterol 2008;103:104–10.
[33] Mazaki T, Ishii Y, Takayama T. Meta-analysis of prophylactic antibiotic use in acute necrotizing pancreatitis. Br J Surg 2006;93:674–84.
[34] Talukdar R, Ingale P, Choudhury HP, et al. Antibiotic use in acute pancreatitis: an Indian multicenter observational study. Indian J Gastroenterol 2014;33:458–65.
[35] McNaught CE, Woodcock NP, Mitchell CJ, et al. Gastric colonisation, intestinal permeability and septic morbidity in acute pancreatitis. Pancreatology 2002;2:463–8.
[36] Tan JW, Gao Y, Kow AWC, et al. Clinical management and outcomes of acute pancreatitis: identifying areas for quality improvement in a tertiary Asian setting. Pancreatology 2019;19:507–18.
[37] Machicado JD, Wani S, Quingalahua E, et al. Practice patterns and adherence to nutrition guidelines in acute pancreatitis: an international physician survey. Pancreatology 2021;21:642–8.
[38] Masamune A, Kikuta K, Hamada S, et al. Clinical practice of acute pancreatitis in Japan: an analysis of nationwide epidemiological survey in 2016. Pancreatology 2020;20:629–36.
[39] Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. Cochrane Database Syst Rev 2012;5:CD009779. https://doi.org/10.1002/14651858.CD009779.pub2.
[40] van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141:1254–63.
[41] Beger HG, Rau B, Isenmann R. Natural history of necrotizing pancreatitis. Pancreatology 2003;3:93–101.
[42] Werge M, Novovic S, Schmidt PN, et al. Infection increases mortality in necrotizing pancreatitis: a systematic review and meta-analysis. Pancreatology 2016;16:698–707.
[43] Krishna SG, Kamboj AK, Hart PA, et al. The changing epidemiology of acute pancreatitis hospitalizations: a decade of trends and the impact of chronic pancreatitis. Pancreas 2017;46:482–8.
[44] Koutroumpakis E, Slivka A, Furlan A, et al. Management and outcomes of acute pancreatitis patients over the last decade: a US tertiary-center experience. Pancreatology 2017;17:32–40.
[45] Trikudanathan G, Wolbrink DRJ, van Santvoort HC, et al. Current concepts in severe acute and necrotizing pancreatitis: an evidence-based approach. Gastroenterology 2019;156:1994–2007.
[46] van Baal MC, van Santvoort HC, Bollen TL, et al. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. Br J Surg 2011;98:18–27.
[47] van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet 2018;391:51–8.
[48] Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307:1053–61.
[49] Ricci C, Pagano N, Ingaldi C, et al. Treatment for infected pancreatic necrosis should be delayed, possibly avoiding an open surgical approach: a systematic review and network meta-analysis. Ann Surg 2021;273:251–7.
[50] Dai W, Zhao Y, Du GL, et al. Comparison of early and delayed cholecystectomy for biliary pancreatitis: a meta-analysis. Surgeon 2021;19:257–62.
[51] Yuan X, Xu B, Wong M, et al. The safety, feasibility, and cost-effectiveness of early laparoscopic cholecystectomy for patients with mild acute biliary pancreatitis: a meta-analysis. Surgeon 2021;19:287–96.
[52] Moody N, Adiamah A, Yanni F, et al. Meta-analysis of randomized clinical trials of early versus delayed cholecystectomy for mild gallstone pancreatitis. Br J Surg 2019;106:1442–51.
[53] van Baal MC, Besselink MG, Bakker OJ, et al. Timing of cholecystectomy after mild biliary pancreatitis: a systematic review. Ann Surg 2012;255:860–6.
[54] Hernandez V, Pascual I, Almela P, et al. Recurrence of acute gallstone pancreatitis and relationship with cholecystectomy or endoscopic sphincterotomy. Am J Gastroenterol 2004;99:2417–23.
[55] Creedon LR, Neophytou C, Leeder PC, et al. Are we meeting the British Society of Gastroenterology guidelines for cholecystectomy post-gallstone pancreatitis? ANZ J Surg 2016;86:1024–7.
[56] Green R, Charman SC, Palser T. Early definitive treatment rate as a quality indicator of care in acute gallstone pancreatitis. Br J Surg 2017;104:1686–94.
[57] Mohy-Ud-Din N, Deyl I, Umar S, et al. Quality gaps in management of acute pancreatitis: a tertiary care center experience. Pancreas 2021;50:544–8.
[58] Aly EA, Milne R, Johnson CD. Non-compliance with national guidelines in the management of acute pancreatitis in the United Kingdom. Dig Surg 2002;19:192–8.
[59] Connor SJ, Lienert AR, Brown LA, et al. Closing the audit loop is necessary to

achieve compliance with evidence-based guidelines in the management of acute pancreatitis. N Z Med J 2008;121:19–25.
[60] Loveday BP, Srinivasa S, Vather R, et al. High quantity and variable quality of guidelines for acute pancreatitis: a systematic review. Am J Gastroenterol 2010;105:1466–76.
[61] Sekimoto M, Takada T, Kawarada Y, et al. JPN Guidelines for the management of acute pancreatitis: epidemiology, etiology, natural history, and outcome predictors in acute pancreatitis. J Hepatobiliary Pancreat Surg 2006;13:10–24.
[62] Westfall JM, Mold J, Fagnan L. Practice-based research–"Blue highways" on the NIH roadmap. JAMA 2007;297:403–6.
[63] Pandanaboyana S, Moir J, Leeds JS, et al. SARS-CoV-2 infection in acute pancreatitis increases disease severity and 30-day mortality: COVID PAN collaborative study. Gut 2021;70:1061–9.