"ProBEISAP: Procalcitonin enhancing BISAP for Early Identification of Severe Acute Pancreatitis - A Multicentric prospective study"

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Sponsor / Sponsor-Investigator	Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
Study Title:	"ProBEISAP: Procalcitonin enhancing BISAP for Early Identification of Severe Acute Pancreatitis - A Multicentric prospective study"
Short Title / Study ID:	ProBEISAP
Protocol Version and Date:	Version 1.0 19/01/2026
Trial registration:	clinicaltrials.gov

PROTOCOL SIGNATURE FORM

Study Title: "ProBEISAP: Procalcitonin enhancing BISAP score for Early Identification of Severe Acute Pancreatitis - A Multicentric prospective study"

The project leader (main center) and the investigator (at the local center/site) have approved the protocol version 1.0 (dated 19.01.2026), and confirm hereby to conduct the project according to the protocol, the Italian legal requirements [1,2], the current version of the World Medical Association Declaration of Helsinki [3] and the principles of Good Clinical Practice.

Project leader (lead center/site) and Sponsor

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Site: Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

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STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Fondazione IRCCS Policlinico San Matteo, Pavia (PV)
Study Title:	"ProBEISAP: Procalcitonin enhancing BISAP for Early Identification of Severe Acute Pancreatitis - A Multicentric prospective study"
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Background and Rationale:	Acute pancreatitis (AP) is an inflammatory disease with a highly variable clinical course. While most patients experience a mild, self-limiting form, approximately 20–30% develop severe acute pancreatitis (SAP), characterized by persistent organ failure and an in-hospital mortality rate of about 15%. In these patients, timely interventions are crucial, therefore considerable efforts have been made to improve early identification of those at risk for SAP. Several prognostic scores have been proposed for this purpose, including APACHE II, Ranson, mCTSI, and BISAP, but none is ideal in terms of accuracy, simplicity and early applicability. Among them, the BISAP score is attractive due to its simplicity, availability at admission, and good predictive performance, although it may still be inferior to other scores in certain contexts. More recently, biomarkers have gained attention for early prediction of disease severity. Procalcitonin (PCT) has shown promising predictive performance; however, as a single biomarker, it does not fully reflect the complex pathophysiology of SAP, limiting its role as a standalone predictor. Based on this evidence, we hypothesize that combining BISAP with PCT may improve early risk stratification. We propose a multicenter prospective study to evaluate the predictive performance of BISAP alone and in combination with PCT measured within 24 and at 36 hours from admission for SAP.

Objective(s):	The primary objective of this study is to evaluate whether the addition of PCT measurements, obtained within 24 hours and at 36 hours from admission, improves the predictive performance of the BISAP score for SAP. The secondary objective of this study is to assess the predictive performance of BISAP combined with PCT for in-hospital mortality, Intensive Care Unit (ICU) admission, organ failure and local complications. An exploratory endpoint will be to identify optimal cut-offs for PCT. Based on the previous objectives, our final aim is to define a new score, the ProBEISAP, for a better stratification of these patients.
Outcome(s):	The primary outcome is the area under the receiver operating characteristic curve (AUC-ROC) derived from the predictive models. Specifically, the AUC-ROC of the models combining the BISAP score with PCT (measure within 24 hours and at 36 hours from admission) will be compared to the AUC-ROC of the BISAP score alone for the prediction of SAP. The secondary outcomes are the AUC-ROC of BISAP combined with PCT for the prediction of in-hospital mortality, ICU admission, organ failure and local complications in comparison to the AUC-ROC of BISAP alone. An exploratory endpoint will be the identification of the optimal PCT cut-off values at 24h, at 36h and for its difference between 36h and 24h for the prediction of SAP. A further exploratory endpoint will be the definition and internal validation of a new score, the ProBEISAP, for a better stratification of these patients.

Study design:	☐ single center study; or X multicenter study; • X coordinated by the proposer --- X observational study ○ ☐ cross-sectional ○ X longitudinal prospective ○ ☐ longitudinal retrospective ○ ☐ laboratory method validation ○ ☐ in vitro study
Inclusion / Exclusion criteria:	This study will include patients with AP. To be eligible for enrollment, patients must be ≥18 years of age, have a confirmed diagnosis of AP according to the revised Atlanta classification and have provided a signed and dated informed consent form. Patients will be excluded if they are pregnant or breastfeeding, or if they have any condition that may alter immune response (e.g. immunodeficiencies) or affect PCT levels (e.g. ongoing infections, antibiotic treatment).
Measurements and procedures:	The investigators will enroll patients consecutively and collect data obtained during routine clinical practice. No additional procedures will be performed. Recorded information will include clinical data, radiological findings, and laboratory results.
Number of Participants with Rationale:	According to published data, the calculated sample size is 910 patients, distributed across the participating sites.
Study Duration:	24 months
Study Schedule:	Recruitment from June 2026 to June 2028
Investigator(s):	See list of centers

Study Centre(s):	Multicenter (see list of centers) Lead center: Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
Statistical Considerations:	Logistic regression models will be used to assess BISAP alone and BISAP combined with PCT as predictors of SAP and secondary outcomes (mortality, ICU admission, organ failure and local complications). Models performance will be evaluated using the AUC-ROC with 95% confidence intervals, and AUCs will be compared using statistical tests for correlated ROC curves (e.g., DeLong's test).
Sample Size	The sample size was calculated for the comparison of two correlated ROC curves. Using published data, the BISAP score AUC was set at 0.875, and the combined BISAP+PCT AUC was expected to be 0.93. Calculations assumed a two-sided α of 0.0017 (Bonferroni correction), β of 0.20 (80% power), and a correlation coefficient of 0.5 between ROC curves. Based on an anticipated SAP incidence of 23% (negative-to-positive ratio 3.29), a total of 910 patients are required, including 212 with SAP and 698 with non-severe AP.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

GLOSSARY OF ABBREVIATIONS

AP	Acute Pancreatitis
AUC	Area Under the Curve
CECT	Contrast-enhanced Computed Tomography
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERCP	Endoscopic Retrograde Cholangiopancreatography
EUS	Endoscopic Ultrasound
ICU	Intensive Care Unit
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
PCT	Procalcitonin
ROC	Receiver Operating Characteristics
SAP	Severe Acute Pancreatitis
SIRS	Systemic Inflammatory Response Syndrome

1. BACKGROUND AND PROJECT RATIONALE

Acute pancreatitis (AP) is an inflammatory condition of the pancreas associated with significant morbidity and mortality.
Globally, the incidence of AP is estimated at 33.7 cases per 100,000 person-years with a mortality rate of 1.6 deaths per 100,000 person-years (4), corresponding to approximately 4.8%.

The most common causes of AP are gallstones and alcohol consumption. Other etiologies include metabolic disorders (e.g. hypercalcemia, hypertriglyceridemia), drug-induced, autoimmune, post–endoscopic retrograde cholangiopancreatography, trauma, infectious, congenital/genetic, and idiopathic forms. With several of these conditions becoming increasingly prevalent, the overall burden of AP is projected to rise (5).

AP can present with varying severity. According to the 2012 revised Atlanta Classification, AP is categorized as mild, moderately severe, or severe.
Mild AP has no organ failure or local/systemic complications and is typically resolved within one week. Moderately severe AP is characterized by transient organ failure, local complications, or exacerbation of comorbid conditions. Severe AP is defined by persistent organ failure lasting more than 48 hours (6).
Most patients experience a mild course, managed with moderate fluid resuscitation, pain and nausea control, and early oral feeding, resulting in rapid improvement. However, 20–30% of patients develop severe AP, a life-threatening condition with in-hospital mortality rates around 15% (7). In these patients, timely and multiple interventions are crucial to improve survival (8).

To facilitate early risk stratification, several scoring systems have been developed, including APACHE II (9), Ranson (10) (31), Glasgow (11), modified CT Severity Index (mCTSI) (30), and BISAP (12).
Among these, Ranson and Glasgow scores require 48 hours for completion, while mCTSI often cannot be calculated on admission because CT is not routinely performed, and peripancreatic necrosis may be detectable only after 72–96 hours (7). APACHE II (9), although accurate, is not specific for AP, requires 12 parameters often unavailable outside Intensive Care Unit (ICU), and is complex to calculate.
To address these limitations, Wu et al. (2008) (12) developed the BISAP score, a simple, easily calculable on admission score, to stratify patients with AP according to their risk of in-hospital mortality. BISAP assigns one point for each of the following presents within the first 24 hours: BUN >25 mg/dL, impaired mental status, systemic inflammatory response syndrome (SIRS), age ≥60 years and pleural effusion.
Validation in a cohort of 18,256 AP patients demonstrated excellent performance, with an area under the curve (AUC) of 0.82 for mortality prediction, comparable to APACHE II (AUC 0.83). Mortality increased progressively with higher BISAP scores: patients with <2 points had <1% mortality, a score

of 2 was associated with 2% mortality, and scores ≥3 correlated with 5–20% mortality. BISAP also reliably predicted mortality in patients without organ failure at admission (AUC 0.79). (12)

Subsequent studies confirmed the utility of BISAP for predicting severity, complications, ICU admission, and mortality across diverse populations (13-15).

For example, a European prospective study reported BISAP AUCs of 0.90 for severe AP (SAP), 0.97 for mortality, and 0.89 for ICU admission, with sensitivities and specificities ranging from 70–100% and 91–93%, respectively, using a cut-off of ≥3 (14).

Meta-analyses and comparative studies showed BISAP is as effective as APACHE II in predicting SAP, mortality and organ failure, and equal or superior to Ranson in several settings (16-18) with reported AUC values for SAP ranging from 0.80 to 0.92 and for mortality from 0.74 to 0.86.

Other studies have reported slightly lower BISAP performance compared with these scores, as well as moderate sensitivity in pooled analyses (20–22), thereby limiting its utility as a standalone predictive score at admission, while nonetheless supporting its role as a valuable triage tool given its aforementioned characteristics.

In SAP, systemic inflammation may progress to multiorgan failure and sepsis, often due to bacterial translocation from the gut (23). Because procalcitonin (PCT) rises in sepsis and bacterial infections (24, 25), it has been evaluated as an early prognostic biomarker in AP.

Studies consistently show that higher PCT levels correlate with disease severity, organ failure, and mortality (16, 26–29). Hagjer et al. (16) reported excellent predictive accuracy (AUCs 0.925 for severity, 0.94 for organ failure, and 0.89 for death), comparable to BISAP and superior to CRP. A recent meta-analysis by Chen and Jiang (27) confirmed the diagnostic value of PCT for severe AP, with pooled sensitivity and specificity above 80%.

Given this evidence, we propose a multicenter prospective study to evaluate the performance of BISAP and BISAP combined with PCT measured within 24 hours from admission and at 36h from admission, for predicting SAP, in-hospital mortality, ICU admission, organ failure and local complications (Appendix 2).

We also plan subgroup analyses to examine potential variations in performance based on age (<60 vs ≥60 years), etiology, and absence of organ failure at admission.

2. PROJECT OBJECTIVES AND DESIGN

2.1. Hypothesis and primary objective (and if applicable also secondary objectives)

PCT has shown promising performance in predicting SAP. However, as a single biomarker, it does not fully capture the complex pathophysiology of the disease.
We hypothesize that combining PCT with the BISAP score will improve early risk stratification and enhance the predictive accuracy of the BISAP score for SAP.

The primary objective of this study is to evaluate whether the addition of PCT measurements, obtained within 24 hours and at 36 hours from admission, improves the predictive performance of the BISAP score for severe acute pancreatitis.

The secondary objective of this study is to assess the predictive performance of BISAP combined with PCT for in-hospital mortality, ICU admission, organ failure and local complications (Appendix 2)

An exploratory endpoint will be to identify optimal cut-offs for PCT.

Based on the previous objectives, our final aim is to define a new score, the ProBEISAP, for a better stratification of these patients.

2.2. Primary and secondary endpoints

Primary endpoint

The primary endpoint is the AUC-ROC derived from the predictive models. Specifically, the AUC-ROC of the models combining the BISAP score with PCT (measure within 24 hours and at 36 hours from admission) will be compared to the AUC-ROC of the BISAP score alone for the prediction of SAP.

Secondary endpoints

The secondary endpoints are the AUC-ROC of BISAP combined with PCT for the prediction of in-hospital mortality, ICU admission, organ failure and local complications in comparison to the AUC-ROC of BISAP alone.

Exploratory endpoints

An exploratory endpoint will be the identification of the optimal PCT cut-off values at 24h, at 36h and for its difference between 36h and 24h for the prediction of SAP.

A further exploratory endpoint will be the definition and internal validation of a new ProBEISAP score for a better stratification of these patients.

2.3. Project design

ProBEISAP is a multicenter, longitudinal prospective observational study on patients with acute pancreatitis.

The aim of this study is to assess whether adding PCT to the validated BISAP score can improve the score's performance in predicting SAP early at admission.

The estimated enrollment period is 24 months, with recruitment planned to start in June 2026 and conclude in June 2028. Patients will be followed up until discharge from the hospital or death, whichever occurs first.

All data are collected as part of the routine clinical practice.
Baseline patient data may be collected at admission in the Emergency Department or in a Surgical or Medical in-patient ward or in the ICU.
If the same variable is recorded more than once within the predefined timeframe (24h), the worst value will be retained.
PCT is collected again at 36 hours.

3. PROJECT POPULATION AND STUDY PROCEDURES

3.1. Project population, inclusion and exclusion criteria

The study will include patients with Acute Pancreatitis.
The total number of patients involved will be 910.

To be eligible for participation in the ProBEISAP study, a patient must meet all of the following criteria at admission:

- Age ≥ 18 years
- Diagnosis of acute pancreatitis (of any etiology) according to the Revised Atlanta Classification (*Box 1*)
- Patient (or legally authorized representative) has provided a signed and dated informed consent form

A patient will be excluded from participation if any of the following conditions is present at admission or documented in medical history:

- Age < 18 years
- Pregnancy or lactation
- Any congenital or acquired immunodeficiency (e.g., primary immunodeficiency, HIV/AIDS) or current pharmacologic immunosuppression (including chronic high-dose corticosteroids or recent use of disease-modifying immunosuppressants)
- Ongoing systemic bacterial infection at admission (intra-abdominal or extra-abdominal), diagnosed on clinical, biochemical, and/or radiological grounds
- Current antibiotic therapy at admission, or completion of systemic antibiotic therapy within the 7 days prior to admission
- Major surgery within 72 hours prior to admission
- Chronic kidney disease stage IV–V or chronic dialysis dependence
- Medullary thyroid carcinoma or other advanced-stage malignancies (defined as metastatic disease or treatment-refractory cancer)
- Known conditions causing ectopic PCT production (e.g., certain neuroendocrine tumors) when documented.
- Any other condition that, in the investigator's judgement, would interfere with interpretation of PCT results.

Box 1. Diagnosis of AP

Diagnostic criteria of Acute Pancreatitis (6)	
Diagnosis of AP requires two of the following three features	
I.	abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back)
II.	serum lipase (or amylase) at least three times greater than the upper limit of normal;
III.	characteristic findings of AP on contrast-enhanced computed tomography (CECT)* or, less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography.
* If the diagnosis of acute pancreatitis is established by abdominal pain and by increases in the serum pancreatic enzyme activities, a CECT is not usually required for diagnosis in the emergency room or on admission to the hospital.	

3.2. Recruitment, screening and informed consent procedure

Patient recruitment will be conducted in the Emergency Department as well as in medical and surgical inpatient wards. The estimated time to complete the enrollment is *24 months.*

Consecutive ongoing recruitment will be performed in daily clinical practice by the project leader or his delegate

The patient will be provided with a participant information sheet and a consent form describing the study and providing sufficient information for them to make an informed decision about their participation. The investigators will explain the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits. Each participant will be informed that participation in the study is voluntary, and they may withdraw from the study at any time without affecting their subsequent medical assistance and treatment. Participants will be given enough time to ask questions and decide whether to participate. The formal consent of a participant will be obtained before the participant enrolment

3.3. Study procedures

Each patient will be followed throughout the hospital stay until discharge or death.

All the following procedures are performed as per clinical routine. No additional procedures are required for patiets for the study beyond normal clinical practice.

See *Appendix 1* for the study flowchart*.*

Enrollment/Baseline Visit - within 24 hours from hospital admission

- Verify that the patient has signed the consent
- Verify inclusion/exclusion criteria
- Record personal information (age, sex, BMI) and date of admission
- Record vitals (respiratory rate, pulse, blood pressure, temperature, SpaO2)
- Record date of symptoms start
- Review medical history (with attention to alcohol abuse) and medication history
- Perform physical examination
- Assess AP etiology: ultrasonography, CECT, MRI, MRCP, EUS or ERCP
- Assess for organ failure as defined by the Marshall scoring system (32)
- Calculate BISAP score as reported in *Box 2*
- Perform blood tests as reported in *Box 3*
- Assess tolerance to oral diet
- Assess pain intensity using the Visual Analog Scale (VAS) (score ranging from 0 to 10)

Box 2. BISAP scoring system

Individual components of the BISAP score	
Assign 1 point to each of the following if:	
Blood Urea Nitrogen (BUN)	> 25mg/dL
Impaired mental status, defined as GCS < 15	Present

Individual components of the BISAP score	
Systemic Inflammatory Response Syndrome (SIRS), defined as presence of two or more of the following: • Temperature <36° or > 38°C • Respiratory rate > 20breaths/min or PaCO2< 32mmHg • Pulse >90 beats/min • WBC < 4000 or >12000 cells/mm3 or >10% immature bands	Present
Age	> 60 years
Pleural effusion detected on imaging	Present
BISAP score: sum of individual items, ranging from 0 to 5 points	

Box 3. Blood tests

Required blood tests	
Complete blood count	Hematocrit Hemoglobin Platelets White blood cell count
Coagulation profile	Fibrinogen
Electrolytes	Sodium (Na+) Potassium (K+) Calcium (Ca2+)
Metabolic profile	Blood glucose Triglycerides
Inflammatory markers	C-reactive protein (CRP) Procalcitonin (PCT)
Pancreatic enzymes	Lipase Amilase

Required blood tests	
Liver function tests	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Lactate dehydrogenase (LDH) Total and direct bilirubin
Renal function	Creatinine Blood Urea Nitrogen (BUN)
Protein Profile	Albumin
ARTERIAL BLOOD GAS ANALYSIS	Lactates pH PaO2 PaCO2 HCO3-

Visit 2 - at 36 hours from admission

- Measure serum PCT levels

Visit 3 - before discharge or at the time of death

- Record occurrence of death.
- Record any ICU admission during the hospital stay.
- Record any local complications identified on CT imaging. (**Appendix 2**)
- Record any organ failure during the hospital stay. (**Appendix 2**)

3.4. Withdrawal and discontinuation

Subjects are free to withdraw from participation in the study at any time upon request. In this case no further data will be acquired for the study.

An investigator may terminate a study subject's participation in the study if the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

This study may be suspended or prematurely terminated if there is sufficient reasonable cause, for instance for insufficient enrolment rate by the participating centers.

4. STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

This prospective study will include adult patients admitted with a diagnosis of Acute Pancreatitis. Data collection will include demographic characteristics, clinical presentation, laboratory findings, imaging data, and in-hospital course. Data will be collected prospectively.

Descriptive statistics will be used to summarize patients. Continuous data will be summarized with the mean and standard deviation or the median and 25^{th}-75^{th} percentiles, depending on the skewness of the distribution; categorical data will be summarized as counts and percentages.

For all analyses, a two-sided p-value <0.05 will be considered statistically significant.

The Stata software (version 19.5 or later, StataCorp, College Station, Texas) will be used for computation.

For each enrolled patient, the BISAP score and the combined BISAP+PCT score will be calculated using values obtained within 24 hours of admission and at 36 hours from admission.

#	Primary Endpoint	Analysis
1	The primary endpoint is the AUC-ROC derived from the predictive models for severe pancreatitis. It will be compared between BISAP alone and BISAP combined with PCT (calculated within 24 hours and at 36 hours from admission) for the prediction of Severe Acute Pancreatitis.	The AUC-ROC will be derived from logistic models using the development of severe acute pancreatitis (SAP) as the dependent variable, and BISAP alone or BISAP+PCT as the independent variable. • PCT will be dichotomized according to the recognized threshold of 0.5 ng/ml. • BISAP will be categorized according to the literature as <2; 2;>=3 The following logistic models will be fitted and compared. 1) Model with BISAP alone 2) Model with BISAP and PCT at 24h 3) Model with BISAP and PCT at 36h The area under the ROC curve of each model will be computed for discrimination and plotted. The comparison of these areas will be

		performed using appropriate statistical tests for correlated ROC curves (e.g., DeLong's test).
	Secondary endpoints	**Analysis**
2.1	The secondary endpoints are the AUC-ROC of BISAP combined with PCT for the prediction of in-hospital mortality, ICU admission, organ failure and local complications in comparison to the AUC-ROC of BISAP alone.	The same analyses as for the primary endpoint will be performed, considering as dependent variables 1) in-hospital mortality 2) ICU admission 3) organ failure 4) local complications
	Exploratory endpoints	
3.1	A further exploratory endpoint will be the identification of an optimal cut-off for PCT at 24h, at 36h and its difference (36-24h) for the prediction of SAP	To identify the optimal cut-off, maximizing the sensitivity and specificity the study cohort will be randomly split into a training set (66%) and a validation set (34%). We will fit the same models described for the EP1 with these identified cut-offs
3.2	A further exploratory endpoint will be the definition and internal validation of a new ProBEISAP score for a better stratification of these patients.	Based on the previous analyses, the best model (highest AUC-ROC) will be used to define the new score by adding PCT as an additional component, by adding 1 point if PCT (or deltaPCT) is above threshold. The performance of ProBEISAP will be evaluated using a testing and validation split of the cohort as described above (internal validation)

Subgroup analyses

Prespecified subgroup analyses of the primary endpoint will be conducted to evaluate the predictive performance of BISAP and BISAP+PCT according to:

- age (<60 vs ≥60 years),
- etiology of acute pancreatitis
  - biliary,

- alcoholic,
- metabolic disorders (hypercalcemia and hypertriglyceridemia)
- others (post RCP, infective, idiopathic)

- absence of organ failure at hospital admission.

An interaction term with the score and the group will be included in the logistic models to assess effect modification.

4.2. Determination of Sample Size

The sample size was calculated based on the comparison of two correlated receiver operating characteristic (ROC) curves.
Using published data, the area under the ROC curve (AUC) of the BISAP score was set as the reference value (AUC = 0.875). We hypothesized that the combined BISAP+PCT score would achieve a significantly higher discriminatory performance, with an expected AUC of 0.93, exceeding the AUC reported for PCT alone in the reference study (AUC = 0.925).

The calculation assumed a two-sided type I error (α) of 0.017 (Bonferroni correction for 3 comparisons) and a type II error (β) of 0.20 (corresponding to a power of 80%). Correlation coefficients between the two ROC curves were assumed to be 0.5 in both the positive (SAP) and negative (non-severe AP) groups. Based on an anticipated incidence of severe acute pancreatitis of 23%, corresponding to a negative-to-positive ratio of 3.29, the required total sample size was estimated to be 910 patients, including approximately 212 patients with SAP and 698 patients with non-severe acute pancreatitis, for a total of 910 patients. This sample size was computed using MedCalc® Statistical Software version 23.4.8 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2026) and confirmed using the Stata command *power tworoc 0.875 0.875 0.93, power(0.80) alpha(0.017) corr(0.50) ratio(3.29)*

4.3. Handling of missing data

We do not plan to perform missing data imputation; we will however compare patients presenting characteristics in whom the score can be computed with those in whom it cannot, due to missingness to exclude a selection bias.

4.4. Biases and confounding

By enrolling consecutive patients satisfying the eligibility criteria, we control for the selection bias. The use of a predefined database built for the purpose of the study with checkboxes or lists, we control for the information bias. The BISAP score being a composite score with relevant patients' characteristics, controls by itself for confounding. The assessment of interaction and subgroup analyses will control effect modification.

5. REGULATORY ASPECTS AND SAFETY

5.1. Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2. Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.3. End of project

Upon project termination, the Ethics Committee is notified within 90 days.

5.4. Insurance

Given the observational nature of the study, it is not necessary to take out a study-specific insurance policy.

6. FURTHER ASPECTS

6.1. Overall ethical considerations

The results of this study will be generalizable to all world population and they could improve knowledge and management of AP.

6.2. Risk-Benefit Assessment

As the study does not include examinations or procedures that are outside clinical practice, participants are not exposed to additional risks arising from participation in the study.

6.3. If applicable: Rationale for the inclusion of vulnerable participants

Not applicable.

7. QUALITY CONTROL AND DATA PROTECTION

7.1. Quality measures

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2. Data recording and source data

All data obtained for this study will be managed using a local regulation compliant Data Management System in accordance with GDPR (General Data Protection Regulation).
These data will be recorded with an Electronic Data Capture (EDC) system using eCRFs.
The REDCap platform (version 15.5.13-© 2026 Vanderbilt University) at the Fondazione IRCCS Policlinico San Matteo, will be used for that purpose.
The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.
Source documents are laboratory and diagnostic reports contained in medical records.

7.3. Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project, in accordance with GDPR. On the CRFs and other project specific documents, patients are only identified by a unique participant number (pseudoanonymization).
It will be the responsibility of the PI to maintain a separate list linking code and patient's identity and his/her unique code.
Each participant in the project will have her/his own username and password and user rights. Accesses and changes are logged within REDCap in a logging trail.

7.4. Retention and destruction of study data and biological material

Study data will be kept for 10 years after the end of the study.

7.5. Funding / Publication / declaration of Interest

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

The ProBEISAP study embraces corporate authorship and all collaborators that contribute to this study will form the ProBEISAP collaborative group.
This group will coauthor all publications in which ProBEISAP study data is used.

8. REFERENCES

1. *Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects)*
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9. APPENDICES

Appendix 1: Study Flowchart

Time	*At admission*	Within 24 h from admission	At 36h from admission	Before discharge or at time of death
Visit	*Screening*	*Baseline Visit*	*Visit 2*	*Visit 3*
Signed consent form *	+			
Assessment of Eligibility criteria *	+			
Record personal information: - ***Age*** - ***Sex*** - ***BMI*** ***And date of admission***		+		
Record vitals: - ***Respiratory rate*** - ***Pulse*** - ***Blood pressure*** - ***Temperature*** - ***SpaO2***		+		
Record date of symptoms start		+		
Review medical and medication history		+		
Perform physical examination		+		
Assess AP etiology		+		
Assess for organ failure		+		
Calculate BISAP score as in Box 2		+		
Perform Blood tests as in Box 3		+	+ ***(record PCT only)***	
Assess tolerance to oral diet		+	+	
Assess pain intensity (VAS)		+	+	
Record occurrence of death				+

Record any ICU admission				+
Record any local complications				+
Record any organ failure				+

* If both of the above conditions are met, proceed with the following procedures

** During the entire hospital stay

Appendix 2: Definitions

I. SEVERITY OF ACUTE PANCREATITIS

The severity of acute pancreatitis (AP) will be classified according to the *2012 Revised Atlanta Classification* (6) as follows:

- **Mild acute pancreatitis**:
  Mild acute pancreatitis is characterized by the absence of organ failure and the absence of local or systemic complications
- **Moderately severe acute pancreatitis**:
  Moderately severe acute pancreatitis is characterized by the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure.
- **Severe acute pancreatitis:**
  Severe acute pancreatitis is characterized by persistent organ failure.

Transient organ failure is organ failure that is present for <48 h.
Persistent organ failure is defined as organ failure that persists for >48 h during the index hospitalization.

For the purpose of this study, severe acute pancreatitis (SAP), defined as persistent organ failure, represents the primary outcome.

II. ORGAN FAILURE

Organ failure will be defined according to the **modified Marshall scoring system** (32).

Organ failure is considered present when a score of **≥2** is recorded in at least one of the following organ systems:

- Respiratory system
- Renal system
- Cardiovascular system

The occurrence, duration, and persistence of organ failure will be recorded throughout the hospital stay.

III. LOCAL COMPLICATIONS

Local complications of acute pancreatitis will be defined according to the **2012 Revised Atlanta Classification** (3) and include:

- Acute peripancreatic fluid collection (APFC)
- Pancreatic pseudocyst
- Acute necrotic collection (ANC)
- Walled-off necrosis (WON)

Other local complications related to acute pancreatitis, such as gastric outlet dysfunction, splenic or portal vein thrombosis, and colonic necrosis, will also be recorded when documented.