Validation and comparison of Scores for Prediction of RIsk for post-operative major Morbidity after cholecystectomy in Acute Calculous Cholecystitis: protocol for a prospective multicenter observational study (SPRIMACC)

Protocol Number:

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the declaration of Helsinki. All personnel involved in the conduct of this study have completed human subjects' protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements.

Principal Investigator: Paola Fugazzola

Signed:  Date: 6/03/2021

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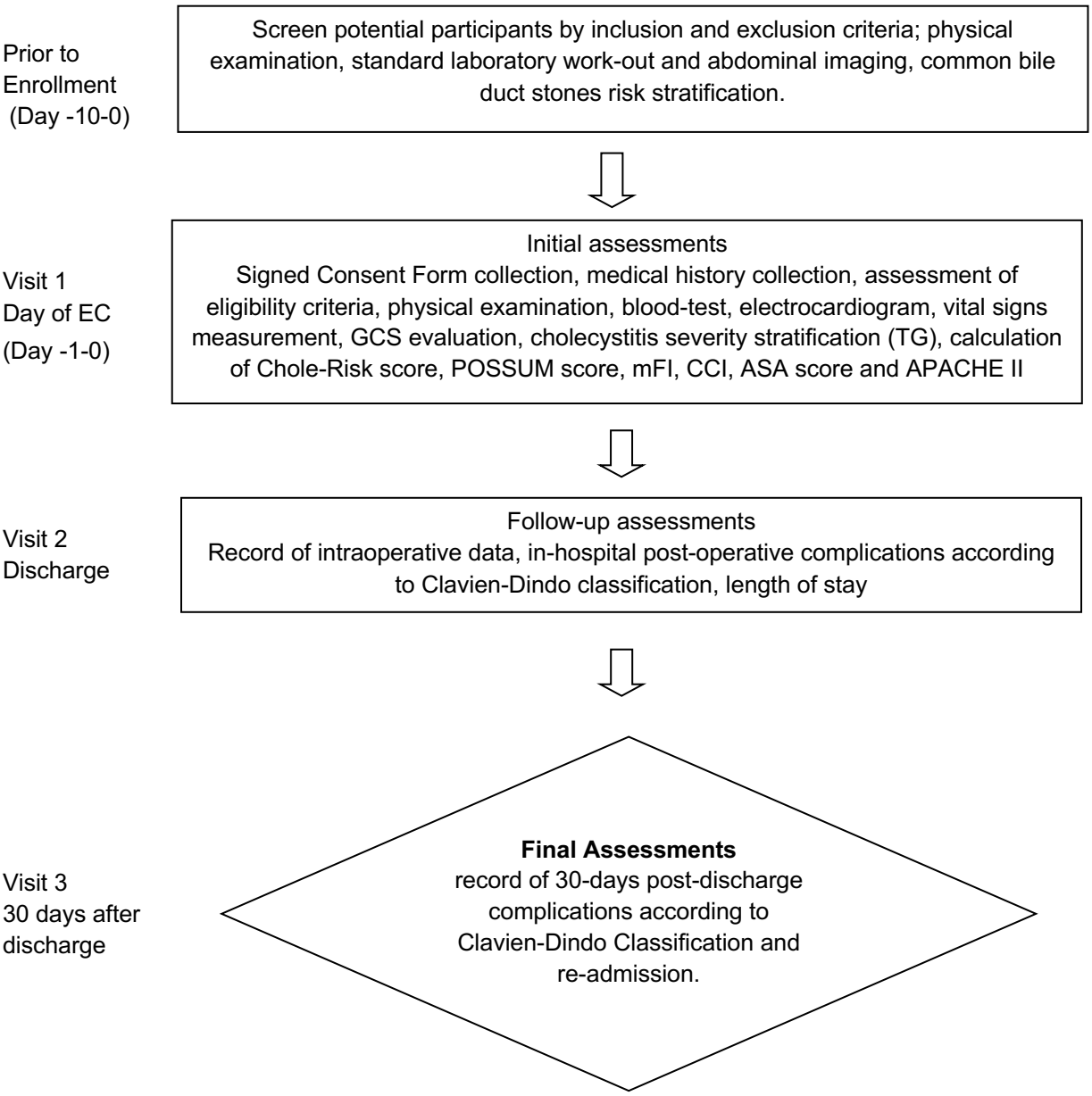
PROTOCOL SUMMARY

Title:	Validation and comparison of Scores for Prediction of RIsk for post-operative major Morbidity after cholecystectomy in Acute Calculous Cholecystitis: protocol for a prospective multicenter observational study (SPRIMACC)
Précis:	Prospective multicentre observational study
Objectives:	Primary: The primary end point is to prospectively validate the Chole-Risk score in predicting a complicated post-operative course (post-operative major complications (Clavien-Dindo≥3a), length of stay (LOS) > 10 days or need of readmission within 30 days from the discharge) in patients undergoing Early Cholecystectomy (EC) for Acute Calculous Cholecystitis (ACC). Secondary: The secondary end point of the study is to prospectively validate and compare the performance of other well-known risk prediction models (the POSSUM/ P-POSSUM score, the Modified Frailty Index (mFI), the Charlson Comorbidity Index (CCI), the American Society of Anesthesiologists (ASA) score and the APACHE II score) in predicting the risk of complicated post-operative course in patients undergoing EC for ACC.
Population:	All consecutive patients presenting with ACC as defined according to the TG 2018 to one of the participating hospitals will be assessed for eligibility on presentation. The calculated sample size is 663 patients.
Study Duration:	18 months
Subject Participation Duration:	30 days after discharge
Estimated Time to Complete Enrollment:	One year

Schematic of Study Design:



1 KEY ROLES AND CONTACT INFORMATION

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The prevalence of gallstones in the general population is 10-15% and the 20-40% of these patients will develop gallstone-related complication (1). According to the third National Health and Nutrition Examination Survey, 6.3 million men and 14.2 million women aged 20 to 74 years old in the United States had gallbladder disease (2). Acute Calculous Cholecystitis (ACC) is the first clinical presentation in 10-15% of patients with gallstone-related complication (1). The Tokyo guidelines (TG) firstly published in 2007 and updated in 2013 and 2018, attempted to establish objective parameters for the diagnosis, classification and management of ACC (3)(4)(5). In 2016 the World Society of Emergency Surgery (WSES) published the first edition of its guidelines for ACC (6), which presented different diagnostic and therapeutic algorithms compared to TG 2013, in particular about diagnostic criteria, severity classification and therapeutic indications. Furthermore, WSES 2016 included discussion on unclear areas like evaluation of the surgical risk of the patients and appropriate management of associated common bile duct stones (CBDS). TG 2018 reached conclusions that were closer to the recommendations of WSES 2016, especially in terms of a more liberal indication for surgery, also for severe ACC (7). However, as reaffirmed in the 2018 updated WSES guidelines (1), some differences from TG 2018 on important topics remains.

At the end of 19th century, precisely in 1882, the first open cholecystectomy was performed by Langenbuch and the removal of gallbladder during the initial hospitalization became the gold standard for symptomatic cholelitiasis (8). With the advent of laparoscopy, laparoscopic cholecystectomy (LC) became the gold standard technique. WSES 16 and WSES20 recommended Early (10 days from symptoms beginning) Laparoscopic Cholecistectomy (ELC) as the first-line therapy for ACC, after a risk stratification for CBDS (1) (7). The only contraindications to ELC are septic shock or absolute anaesthesiology contraindications. ELC is recommended also for patients with Child A and B cirrhosis, advanced age and patients who are pregnant. WSES20 recommended laparoscopic or open subtotal cholecystectomy in situations in which anatomic identification is difficult and in which the risk of iatrogenic injuries is high.

TG suggest the following treatment flowchart (7):

- **a.** Grade I ACC: ELC is recommended if the CCI and ASA-PS scores suggest the patient can withstand surgery (CCI<6 and ASA-PS<3). If patient cannot withstand surgery, TG 18 suggested conservative management and to consider DLC.
- **b.** Grade II ACC: ELC in an advanced surgical center is recommended if the CCI and ASA-PS scores suggest the patient can withstand surgery (CCI<6 and ASA-PS<3). In case of difficult cholecystectomy, switch to open or subtotal cholecystectomy could be considered. If patient cannot withstand surgery, TG 18 suggested conservative management and, if patient does not respond to initial medical treatment, biliary drainage (BD) (consider DLC).

c. Grade III ACC: Attempts should be made to normalize organ function through organ support, alongside administration of antimicrobials. ELC in an advanced surgical center is recommended if the patient is judged to be able to withstand surgery (no neurological and respiratory dysfunction, total bilirubin <2 mg/dL, CCI<4 and ASA-PS <3). In case of difficult cholecystectomy, switch to open or subtotal cholecystectomy could be considered. If patient cannot withstand surgery, TG 18 suggested conservative management and, if patient does not respond to initial medical treatment, biliary drainage (BD) (consider DLC).

Focusing on timing of cholecystectomy, TG18 recommended ELC regardless of exactly how much time has passed since onset. Comparing ELC and Delayed Laparosocpic Cholecistestomy (DLC), ELC (both within 72 hours and within 1 week) showed shorter total hospital stays and lower costs (8). WSES20 recommended ELC to be performed as soon as possible, within 7 days from hospital admission and within 10 days from the onset of symptoms. In case ELC cannot be performed within this timing, DLC beyond 6 weeks should be preferred.

WSES 2020 suggested to consider non operative management (NOM) for patients refusing surgery or for those who are not suitable for surgery. The NOM could include the best medical therapy with antibiotics and observation and, if initial NOM fails, alternative treatment options, like BD. BD decompresses the infected bile or pus in the gallbladder, removing the infected collection without removing the gallbladder. The removal of the infected material, in addition to antimicrobial therapy, can result in a reduced inflammation with an improvement of the clinical condition (6). A recent randomized controlled trial (CHOCOLATE) (9) compared ELC and percutaneous gallbladder drainage (PTGBD) in high risk patients (APACHE II score $\geq$ 7) with ACC and showed an higher major complication rate, an higher reintervention rate and an higher rate of recurrent biliary disease in PTGBD. However, besides PTGBD, non-surgical approaches may include several other endoscopic procedures, that can be considered an alternative to PTGBD in high-risk patients with ACC. Among these, alternative options are endoscopic transpapillary gallbladder drainage (ETGBD), with placement of a transpapillary naso-gallbladder drainage tube (ENGBD) or double-pigtail stent (EGBS), or transmural ultrasound-guided gallbladder drainage (TUGD). According to WSES 2020, ETGBD or EUS-GBD could be considered safe and effective alternatives to PTGBD (1). A recent randomized controlled trial (DRAC 1) (10) compared EUS-GBD with PTGBD in high risk patients (age$\geq$80, ASA-PS score$\geq$3, age-adjusted CCI>5 or Karnofsky score <50) with ACC, finding improved outcomes in EUS-GBD (lower 1-year and 30-days adverse events, lower reintervention rate, lower rate of unplanned readmissions, lower rate of recurrent cholecystitis, lower pain and analgesic requirements). Furthermore, EUS-GBD with lumen-apposing self-expandable metal stents (LAMSs) should be preferred to ETGBD, with removal of metal stent within 4 weeks (1).

TG 2013 did not consider issues like physical status such as co-morbidities in the decision process in the management of ACC, and, until TG 2018, Grade III ACC was considered not suitable for surgery. TG 2018 introduced a modified flowchart, more similar to the WSES 2016, based on more recent evidences, and recommended that the treatment strategy would be chosen after an assessment of cholecystitis severity, the patient's general status and underlying disease.

To evaluate the patient's comorbidity and general status, TG18 suggested to use the Charlson comorbidity index (CCI) and the American Society of Anesthesiologists physical status classification (ASA-PS).

Recently, some risk prediction models have been proposed, but they are lacking of a prospective validation.
In particular, Di Martino et al. (11) created a quite simple and easily reproducible score (**the Chole-risk Score**) for predict increased 30-day major morbidity (Clavien-Dindo≥3a), prolonged length of stay and risk of readmission within 30 days after ELC for ACC. The Chole-Risk Score was developed using four groups of pre-operative variables: (a) previous abdominal interventions such as previous abdominal surgery and previous percutaneous cholecystostomy, (b) patient comorbidities such as diabetes and CCI > 6, (c) predictors of concomitant bile duct disease such as increased total bilirubin > 2 mg/dL and dilated bile duct and (d) predictors of difficult cholecystectomy such as perforated gallbladder and severity grade (1 vs 2-3 according to TG18). Each group could score either 0 or 1 if any variables resulted positive. Therefore, Chole-Risk Score ranged from 0 to 4 (Table 1). It presented a progressive increase in postoperative complications ranging from 5.8% of patients scoring 0 to 47.8% of patients scoring 4. The score with its risk assessment was made available online at https://www.calconic.com/ calculator-widgets/cholerisk/5f00380606e42a00296f59de? layouts=true.
The model was validated only by an internal retrospective validation analysis.

Table 1. The Chole-Risk score

	Pre-operative variables:	Score
A)	previous abdominal interventions such as previous abdominal surgery and previous percutaneous cholecystostomy	1
B)	patient comorbidities such as diabetes and CCI > 6	1
C)	predictors of concomitant bile duct disease such as increased total bilirubin > 2 mg/dL and dilated bile duct	1
D)	predictors of difficult cholecystectomy such as perforated gallbladder and severity grade (1 vs 2-3 according to TG18)	1

The Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (**POSSUM**) was proposed by Copeland et al in 1991 (12) as a method for normalizing patient data so the direct comparison of patient outcome could be made. It includes a Physiological Score (PS) (Table 2a) and an Operative severity Score (OS) calculated at the time of surgery (Table 2b). These scores are then inserted into two formulas (12) and risks of both mortality and morbidity can be predicted for the workload of each surgical team. Because it was found that the published

POSSUM predictor equation for mortality overpredicted deaths, the Portmouth POSSUM (**P-POSSUM**) equation was introduced to reach a more reliable prediction of mortality (13)(14). POSSUM and P-POSSUM scores have been validated for hepato-biliary-pancreatic surgery (15) (16), gastric surgery (17), colorectal surgery (18) and for emergency laparotomies (19). Sato et al. (20) applied POSSUM score to patients with ACC underwent ELC and found that a POSSUM score ≥48.3 was an independent factor for postoperative complications. González-Muñoz et al (21), in a prospective cohort study including 149 patients with ACC treated with ELC or with medical therapy, found that the only independent predictors of death at the time of admission were the degree of cholecystitis and the P-POSSUM score. Unfortunately even a formal prospective validation of POSSUM and P-POSSUM for ELC in patients with ACC is lacking.

Table 2. The POSSUM score: a) Physiological Score; b) Operative severity Score

a)

	Score			
	1	2	4	8
Age (years)	⩽60	61–70	⩾71	
Cardiac signs	No failure	Diuretic, digoxin, antianginal or hypertensive therapy	Peripheral oedema; warfarin therapy	Raised jugular venous pressure
Chest radiograph			Borderline cardiomegaly	Cardiomegaly
Respiratory history	No dyspnoea	Dyspnoea on exertion	Limiting dyspnoea (one flight)	Dyspnoea at rest (rate ⩾30/min)
Chest radiograph		Mild COAD	Moderate COAD	Fibrosis or consolidation
Blood pressure (systolic) (mmHg)	110–130	131–170 100–109	⩾171 90–99	– ⩽89
Pulse (beats/min)	50–80	81–100 40–49	101–120	⩾121 ⩽39
Glasgow coma score	15	12–14	9–11	⩽8
Haemoglobin (g/100 ml)	13–16	11·5–12·9 16·1–17·0	10·0–11·4 17·1–18·0	⩽9·9 ⩾18·1
White cell count ($\times 10^{12}$/l)	4–10	10·1–20·0 3·1–4·0	⩾20·1 ⩽3·0	
Urea (mmol/l)	⩽7·5	7·6–10·0	10·1–15·0	⩾15·1
Sodium (mmol/l)	⩾136	131–135	126–130	⩽125
Potassium (mmol/l)	3·5–5·0	3·2–3·4 5·1–5·3	2·9–3·1 5·4–5·9	⩽2·8 ⩾6·0
Electrocardiogram	Normal		Atrial fibrillation (rate 60–90)	Any other abnormal rhythm or ⩾5 ectopics/min Q waves or ST/T wave changes

COAD, chronic obstructive airways disease

b)

	Score			
	1	2	4	8
Operative severity*	Minor	Moderate	Major	Major+
Multiple procedures	1		2	>2
Total blood loss (ml)	⩽100	101–500	501–999	⩾1000
Peritoneal soiling	None	Minor (serous fluid)	Local pus	Free bowel content, pus or blood
Presence of malignancy	None	Primary only	Nodal metastases	Distant metastases
Mode of surgery	Elective		Emergency resuscitation of >2 h possible† Operation <24 h after admission	Emergency (immediate surgery <2 h needed)

* Surgery of moderate severity includes appendicectomy, cholecystectomy, mastectomy, transurethral resection of prostate; major surgery includes any laparotomy, bowel resection, cholecystectomy with choledochotomy, peripheral vascular procedure or major amputation; major+ surgery includes any aortic procedure, abdominoperineal resection, pancreatic or liver resection, oesophagogastrectomy; † indicates that resuscitation is possible even if this period is not actually utilized

Fagenson et al (22) retrospectively stratified 6898 patients with ACC who underwent ELC using the **modified Frailty Index (mFI)**. They found that Clavien IV complications and mortality were higher for intermediate-frail patients and high-frail patients and mFI had excellent accuracy for mortality (AUC=0.83) and Clavien IV complications (AUC=0.73). Frailty is an established method used to study outcomes in surgery. One of the most widely used frailty assessment tools is the frailty index from the Canadian Study on Health and Aging (CSHA) (23). In 2013, Velanovich et al (24) described a simplified edition of the CSHA frailty index, created by mapping the variables in the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) database used to calculate the CSHA score. The mFI consists of 11 preoperative variables. One point was allotted for each of the following preoperative comorbidities: (1) patient functional status before surgery partially or totally dependent; (2) diabetes mellitus treated with insulin or oral medications; (3) hypertension requiring treatment; (4) congestive heart failure (CHF); (5) myocardial infarction (MI); (6) prior cardiac surgery or percutaneous coronary angioplasty, or history of angina; (7) chronic obstructive pulmonary disease (COPD) or pneumonia; (8) rest pain or gangrene secondary to peripheral vascular disease (PVD) or PVD treated with angioplasty, revascularization, amputation; (9) impaired sensorium within 48 h prior to the surgical procedure not in the context of concomitant neurologic disease such as dementia; (10) history of transient ischemic attack (TIA) or cerebrovascular accident (CVA) without neurologic deficits; and (11) CVA with neurologic deficits. Possible mFI values range from 0 to 11. Patients could be classified as non-frail (mFI 0), low frailty (mFI 1–2), intermediate frailty (mFI 3–4), or high frailty (mFI ≥ 5) (Table 3).

Table 3. The modified Frailty Index

©	Pre-operative variables	Score
A)	patient functional status before surgery partially or totally dependent	1

B)	diabetes mellitus treated with insulin or oral medications	1
C)	hypertension requiring treatment	1
D)	congestive heart failure (CHF)	1
E)	myocardial infarction (MI)	1
F)	prior cardiac surgery or percutaneous coronary angioplasty, or history of angina	1
G)	chronic obstructive pulmonary disease (COPD) or pneumonia	1
H)	rest pain or gangrene secondary to peripheral vascular disease (PVD) or PVD treated with angioplasty, revascularization, amputation	1
I)	impaired sensorium within 48 h prior to the surgical procedure not in the context of concomitant neurologic disease such as dementia	1
L)	history of transient ischemic attack (TIA) or cerebrovascular accident (CVA) without neurologic deficits	1
M)	CVA with neurologic deficits	1

Endo et al (25), in a retrospective multicenter study on 5329 patients with ACC treated with cholecystectomy and/or gallbladder drainage, found that among patients who underwent cholecystectomy there was a statistical significant step-up of the mortality rates between patients with a **Charlson Comorbidity Index (CCI)** below 6 and 6 or higer. CCI was created by Charlson et al in 1987 (26) for classifying comorbid conditions which might alter the risk of mortality for use in longitudinal studies. Comorbid conditions with a weight of one include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, ulcer disease, mild liver disease, and diabetes mellitus. Diabetes mellitus with end organ damage, any tumor, leukemia, and lymphoma have a weight of two. Moderate or severe liver disease has a weight of three. Metastatic solid tumors and AIDS have a weight of six. The total score is calculated by adding the weights.

Table 4. Charlson Comorbidity Index (CCI)

Score	Condition
1	
	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥ 6 cm)
	Cerebrovascular disease: accident with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	
	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 years from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	
	Moderate or severe liver disease
6	
	Metastatic solid tumor
	AIDS (not just HIV positive)

TIA: transient ischemic attacks; HIV: human immunodeficiency virus.

A systematic review and meta-analysis of studies reporting on the ability of prognostic factors or risk prediction models to predict outcomes in patients with ACC after ELC, showed that, up to now, there are not reliable models (27). The only available comparison of risk assessment scores (ASA (Table 5), APACHE II (Table 6) and POSSUM) is limited to the perforated ACC and it highlights a significant association of the three scores with morbidity and mortality. APACHE II seems to be the best risk predictor (28), but it is built to predict morbidity and mortality in the patients admitted to ICU: its use as a preoperative score should be considered as an extension usage from the original concept. Then, WSES 2020 did not suggest the use of any prognostic model in patients with ACC (1).

Table 5. ASA (American Society of Anesthesiologists) grade of physical status

Category	Physical Status
ASA 1	Normal healthy patient
ASA 2	Patient with mild systemic disease
ASA 3	Patient with severe systemic disease that is not a constant threat to life
ASA 4	Patient with severe systemic disease that is a constant threat to life
ASA 5	Moribund patient not expected to survive with or without surgery

Table 6. Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II)

	Physiologic variable[b]	Point score								
		+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature	⩾41°	39–40.9°	–	38.5–38.9°	36–38.4°	34–35.9°	32–33.9°	30–31.9°	⩽29.9°
2	Mean arterial pressure (mm Hg)	⩾160	130–159	110–129	–	70–109	–	50–69	–	⩽49
3	Heart rate	⩾180	140–179	110–139	–	70–109	–	55–69	40–54	⩽39
4	Respiratory rate(non-ventilated or ventilated)	⩾50	35–49	–	25–34	12–24	10–11	6-9	–	⩽5
5	Oxygenation:									
	a) FiO_2 ⩾ 0.5: use A-aDO_2	⩾500	350–499	200–349	–	<200	–	–	–	–
	b) FiO_2 < 0.5: use PaO_2 (mm Hg)	–	–	–	–	>70	61–70	–	55–60	<55
6	Arterial pH	⩾7.7	7.6–7.69	–	7.5–7.59	7.33–7.49	–	7.25–7.32	7.15–7.24	<7.15
7	Serum Na (mMol/L)	⩾180	160–179	155–159	150–154	130–149	–	120–129	111–119	⩽110
8	Serum K (mMol/L)	⩾7	6–6.9	–	5.5–5.9	3.5-5.4	3–3.4	2.5–2.9	–	<2.5
9	Serum creatinine (mg/dL): double point score for acute renal failure	⩾++++3.5	2–3.4	1.5–1.9	–	0.6–1.4	–	<0.6	–	––
10	Hct (%)	⩾60	–	50–59.9	46–49.9	30–45.9	–	20–29.9	–	<20
11	WBC (in l000s)	⩾40	–	20–39.9	15–19.9	3–14.9	–	1–2.9	–	<1
12	Glasgow coma score (GCS)	Score = 15 minus actual GCS								
Acute physiology score is the sum of the 12 individual variable points										
Add 0 points for the age <44.2 points. 45–54 years: three points. 55–64 years: five points. 65–74 years: six points ⩾75 years										
APACHE II score = acute physiology score + age points + chronic health points. Minimum score = 0; maximum score = 71. Increasing score is associated with increasinf = g risk of hospital death										
Add chronic health ststus points: two points if elective postoperative patient with immunocompromise or history of severe organ insufficiency: five points for nonoperative patient or emergency postperative patient with immunocompromise or severe organ insufficiency[c]										
13[d]	Serum HCO_3(venous-mMol/L) use only if no ABGs52	⩾52	41–51.9	–	32–40.9	22–31.9	–	18–21.9	15–17.9	<15

Adapted from Knaus WA. Draper EA. Wagner DP. Zimmermam JB: APACHE II: A severity of disease classification system. *Critial care medicine* 13: 818–829. 1985.
Interpretation of APACHE II scores (predicted mortality rate).
0–4 = ~4% death rate 10–14 = ~15% death rate 20–24 = ~40% death rate 30–34 = ~75% death rate.
5–9 = ~8% death rate 15–19 = ~25% death rate 25–29 = ~55% death rate Over 34 = ~85% death rate.

[a] APACHE II Score = acute physiology score + age points + chronic health points. Minimum score = 0; maximum score = 71. Increasing score is associated with increasing risk of hospital death.

[b] Choose worst value in the past 24 h.

[c] Chronic health status: Organ sufficiency (e.g. hepatic, cardiovascular, renal, pulmonary) or immuno-compromised state must have preceded current admission.

[d] Optional variable: use only if no ABGs.

In 2017, the WSES joined the Italian Society for Geriatric Surgery during a consensus conference regarding the management of ACC in the elderly, with the aim of investigating this subgroup of fragile patients, considered at 'very high risk' for surgery. Despite the unanimous concordance in supporting the surgical management of ACC in the elderly and in refusing old age by itself as a contraindication for surgery, the authors found a substantial lack of high quality studies on the topic (29).

2.2 Rationale

Considering the possibility to offer more conservative treatments than EC in high-risk patients with ACC, it would be necessary to stratify the risk of post-operatory complications and mortality after EC, in order to give to clinicians and to patients more tools to choose the best treatment for each patient.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Study participants have no potential risks arising from the study.

2.3.2 Potential Benefits

Results of present study could improve knowledge and management of ACC.

3 OBJECTIVES

3.1 Study Objectives

The SPRIMACC study is a prospective multicenter observational study with the primary endpoint to prospectively validate the Chole-Risk score in predicting a complicated post-operative course (post-operative major complications (Clavien-Dindo≥3a), length of stay (LOS) > 10 days or need of readmission within 30 days from the discharge) in patients undergoing Early Cholecystectomy (EC) for Acute Calculous Cholecystitis (ACC). The secondary endpoints of the study are to prospectively validate and compare other well-known risk prediction models (the POSSUM/P-POSSUM score, the Modified Frailty Index (mFI), the Charlson Comorbidity Index (CCI), the American Society of Anesthesiologists (ASA) score and the APACHE II score) in predicting a complicated post-operative course in patients undergoing EC.
The Chole-Risk score, the POSSUM score, the mFI, the CCI, the ASA score and the APACHE II score are reported in Table 1-6.

3.2 Study Outcome Measures

The study outcome is a composite outcome including:

- 30-day post-operative major morbidity, intended as Clavien-Dindo ≥3a complication (Clavien-Dindo classification is reported in table 7),
- length of stay (LOS) > 10 days
- readmission within 30 days from the discharge

after EC for ACC.

Table 7. Clavien-Dindo classification of surgical complications

1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions, antibiotics and total parenteral nutrition are also included
3	Requiring surgical, endoscopic or radiological intervention

3a	Intervention under regional/local anesthesia
3b	Intervention under general anesthesia
4	Life-threatening complication requiring intensive care/intensive care unit management
4a	Single-organ dysfunction
4b	Multi-organ dysfunction
5	Patient death

In order to assess prediction accuracy of the analyzed prediction models for the outcome, receiver operating characteristic (ROC) curves will be generated for each scoring system, with sensitivity plotted on the Y-axis and specificity plotted on the X-axis. The area under the ROC curve (AUC) is considered to be a reliable method for examining the properties of a diagnostic test and will be used to compare the diagnostic abilities of the scoring systems.

The observed-to-expected (O/E) operative morbidity (mortality) ratio will be calculated, with the O/E value representing the ratio of actual mortality (mortality) to measured (predicted) morbidity (mortality). An O/E value of 1 indicates ideal predictive ability of a scoring system. An O/E ratio <1 indicates lower morbidity than expected, while an O/E ratio >1 indicates greater morbidity than expected.

4 STUDY DESIGN

SPRIMACC is a prospective multicenter observational study on patients with ACC candidate to EC. The rationale of the study is to validate and compare existing risk prediction models for complicated port-operative course in this population. The calculated sample size is 663 patients. The approximate time to complete enrollment is one years and the duration of subject participation 30 days from discharge. In general EC will be performed according to the local hospital practice. In particular ELC will be performed by the four-trocar technique with transection of the cystic duct and cystic artery after reaching the critical view of safety. ELC will be performed by a surgeon trained and experienced in laparoscopic surgery defined as > 5 laparoscopic procedures for ACC on a yearly basis. Patients may receive prophylactic antibiotics according to the local hospital protocol. Antibiotic therapy will not be routinely continued post-operatively unless the performing surgeon has strong indications to do so (such as (imminent) sepsis or hemodynamic instability). In these cases, the primary investigator will be notified and the indications have to be well documented.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- have a diagnosis of ACC as defined by TG18 criteria (Table 9)
- be ACC candidate to EC during the index admission*
- be ≥ 18 years old
- be stratified for the risk of CBDS according to the Israelian Score (30), and, in case of confirmation of CBDS receive pre-operative ERCP
- provide signed and dated informed consent form
- willing to comply with all study procedures and be available for the duration of the study.

* All the patients treated with initial open cholecystectomy, those who undergo ELC, those with conversion from laparoscopic to open cholecystectomy or those who undergo bail out procedures (e.g. subtotal cholecystectomy) will be included.

Table 9 Diagnostic criteria for Acute Calculous Cholecystitis according to TG18

A) Local signs of inflammation
1. Murphy's sign 2. RUQ mass, pain or tenderness
B) Systemic signs of inflammation
1. Fever 2. elevated CRP 3. elevated WBC count
C) Imaging Findings
Imaging findings characteristic of acute cholecystitis
Definite diagnosis
One item in A + one item in B + C

RUQ: right upper quadrant, CRP: C reactive protein, WBC: white blood cells; modified from reference (5).

5.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- pregnancy or lactation
- acute cholecystitis not related to a gallstone etiology
- onset of symptoms >10 days before cholecystectomy**
- concomitant cholangitis or pancreatitis
- intraoperative treatment of common bile duct stones
- anything that would place the individual at increased risk or preclude the individual's full compliance with or completion of the study.

** Patients with ACC associated with common bile duct stones who underwent pre-operative ERCP could be included if they receive EC within 10 days from onset of symptoms

5.3 Strategies for Recruitment and Retention

Recruitment will take place during hospitalization. Participants will not be compensated for study participation. Participants will be contacted by phone 30 days after EC.

5.4 Subject Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject's participation in the study if:

- Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.5 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the Ethics Board (EB) and will provide the reason(s) for suspension or termination.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

6 STUDY SCHEDULE

6.1 Screening

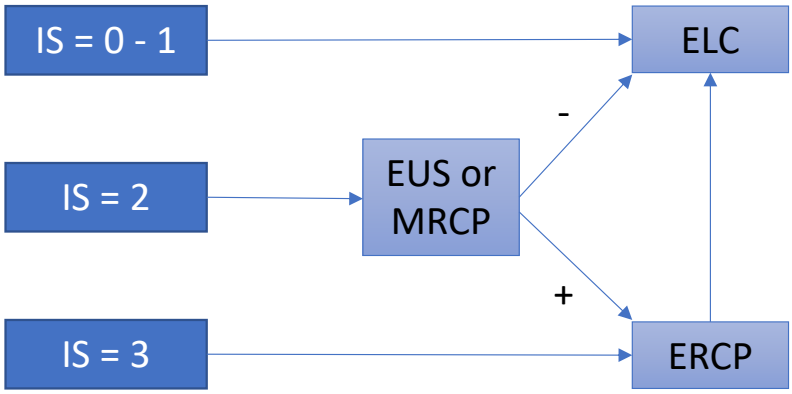
Screening Visit (Day -10 to 0)

- Assessment of eligibility based on inclusion/exclusion criteria.
- Perform physical examinations needed to determine eligibility.
- Perform blood examination (blood count, C-reactive protein, liver function test)
- An abdomen ultrasound will be performed to confirm the diagnosis. If the findings on ultrasound examination are inconclusive, a contrast enhanced CT-scan or a Magnetic Resonance (MR) of the abdomen will be eventually performed
- Stratify the risk of Common Bile Duct Stone (CBDS) according to Israelian Score (IS) ideated and validated on patients with ACC by Khoury et al (30) (Table 8, Fig. 1). In case of IS equal to 2, the patient should undergo preferentially a preoperative endoscopic ultrasound (EUS) or a Magnetic Resonance Cholangio-Pancreatography (MRCP) to investigate CBDS. In case of confirmation of CBDS or in case of IS equal to 3, an Endoscopic retrograde cholangiopancreatography (ERCP) prior to ELC should be performed. In case of score equal to 0 or 1, the patient could be directly subjected to ELC.

Table 8. Israelian Score for the risk of CBDS in ACC.

Predictive Factor for choledocholithiasis	
Parameters	**Score**
CBD width by US ≥ 7mm	1
Age (years) ≥ 70	1
Total bilirubin ≥ 1.8	1

Figure 1. Screening for CBDS in ACC (IS: Israelian Score; EUS: endoscopic ultrasound; MRCP: Magnetic Resonance Cholangio-Pancreatography; ELC: Early Laparoscopic Cholecistectomy; ERCP: Endoscopic retrograde cholangiopancreatography).



6.2 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 1, Day of EC, Day -1-0)

- Obtain and document consent from participant on study consent form.
- Verify inclusion/exclusion criteria, in particular less then 10 days from onset of symptoms.
- Review medical and medication history.
- Assess functional status
- Physical examination
- Perform blood test (blood count, C reactive protein, liver function test, urea, Na, K, creatinine, ABGs, PT-INR, PCT) and electrocardiogram
- Record vital signs (blood pressure, pulse, temperature, respiratory rate)

- Evaluate Glasgow Coma Scale (GCS)
- Calculate Chole-risk score, POSSUM score§, mFI, CCI, ASA score and Apache II score. (§For POSSUM Score for EC operative severity is “moderate”, number of procedure 1, blood loss <100mL).
- Stratify Cholecystitis severity according to TG 2018 (Table 9).

Table 9. TG 2018 Classification of ACC

Grade III, Severe ACC:	ACC associated with organ dysfunction a. Cardiovascular dysfunction: Hypotension with dopamine >5 µg/kg per min, or Norepinephrine, any dose; b. Neurological dysfunction: Decreased level of consciousness; c. Respiratory dysfunction: PaO2/FiO2 ratio<300; d. Renal dysfunction: Oliguria, creatinine>2.0 mg/dl; e. Hepatic dysfunction: PT-INR>1.5; f. Hematological dysfunction: Platelet count <100,000/mm3.
Grade II, Moderate ACC	ACC associated with any one of the following conditions: a. Elevated white blood cell count (>18,000/mm3); b. Palpable tender mass in the right upper abdominal quadrant; c. Duration of complaints >72 h; d. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis).
Grade I, Mild ACC	ACC which does not meet the criteria of ‘‘Grade III’’ or ‘‘Grade II’’ ACC: grade I can also be defined as AC in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

6.3 Intermediate Visits

Visit 2, Day of discharge

- Record intraoperative data (operative time, need to open conversion, intraoperative complication, intraoperative death, bail-out procedures)
- Record complications occurred in the post-operatory period and classify them according to Clavien-Dindo classification (Table 7)
- Record length of postoperative hospital stay

6.4 Final Study Visit

Follow-up by phone (Final Visit, Day 30 after discharge)

- Record complications occurred in the post-discharge period and classify them according to Clavien-Dindo classification (Table 7).
- Record re-admission and reasons for re-admission

7 STUDY PROCEDURES/EVALUATIONS

7.1 Study Procedures/Evaluations

All procedures/evaluation are part of normal standard of clinical care

7.2 Laboratory Procedures/Evaluations

All laboratory procedures/evaluation are part of normal standard of clinical care

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

Safety monitoring for this study will focus on unanticipated problems involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event.

8.1.1 Unanticipated Problems

It is considered an unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the EB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.2 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical

judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2 Reporting Procedures

Incidents or events that meet the criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. Investigators should include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the EB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the EB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the EB within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the EB within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), within one month of the EB's receipt of the report of the problem from the investigator.

9 STUDY OVERSIGHT

The investigator will be responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. The PI will review the data for safety concerns and data trends at regular intervals, and will promptly report to the EB any Unanticipated Problem (UP), protocol deviation, or any other significant event that arises during the conduct of the study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Considerations

Sample size requirements for prospective validation studies of prognostic scores are not well understood. The limited empirical evidence to support investigators in guiding their sample size choice for validation studies suggests a minimum of 100 events and 100 nonevents (31)(32)(33). The sample size calculation has been obtained considering that in the 2021 Di Martino trial the rate of patients with post-operative Clavien-Dindo≥3a complications or with a post-operative LOS>10 days or who required readmission within 30 days from the surgical intervention after EC for ACC was 15,1% (282/1868). According to these data to reach 100 events, 563 nonevents would be required, with a total of 663 patients.

10.2 Final Analysis Plan

In order to assess prediction accuracy, receiver operating characteristic (ROC) curves will be generated for each scoring system, with sensitivity plotted on the Y-axis and specificity plotted on the X-axis. The area under the ROC curve (AUC) is considered to be a more reliable method for examining the properties of a diagnostic test and will be used to compare the diagnostic abilities of the scoring systems.
The observed-to-expected (O/E) operative morbidity (mortality) ratio will be calculated, with the O/E value representing the ratio of actual mortality (mortality) to measured (predicted) morbidity (mortality). An O/E value of 1 indicates ideal predictive ability of a scoring system. An O/E ratio <1 indicates lower morbidity than expected, while an O/E ratio >1 indicates greater morbidity than expected.
For nominal data the Chi-Square test will be used. For continuous data and counts the independent sample t-test or one-way ANOVA will be used.
Results will be presented as odds ratios with a corresponding 95% confidence interval. A two-tailed $p < 0.05$ is considered statistically significant.

The manuscript reporting the SPRIMACC trial results will adhere with TRIPOD guidelines/methodology.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

The SPRIMACC trial will be conducted in accordance with the declaration of Helsinki.
The study protocol will be approved by the medical EB of the trial coordinating centre at the IRCCS San Matteo hospital, Pavia (Italy).
Secondary approval will be obtained from all local ethics committees in the participating centres.
Patients will give oral as well as written informed consent prior to inclusion.

12.2 Institutional Review Board

Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the medical EB before the changes are implemented in the study.

12.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be EB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

12.4 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators and study staff.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval.

13 DATA HANDLING AND RECORD KEEPING

13.1 Database system

Data will be collected and stored online through a secure server.

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

13.2 Case Report Form (CRF)

A detailed CRF is created and provided to the invited centers (see also appendix C).

13.3 Data Privacy statement

All anonymous study data will be available to the SPRIMACC study team. The data of a center will be available to that specific center only through the database system website. The data will not contain identifiable patient parameters (e.g. no date of birth etc.) in compliance with the General Data Protection Regulation (GDPR - EU 2016/679) and with the D.Lgs. 196/2003 (“Codice italiano in materia di protezione dei dati”). Each patient will be coded with a unique patient number so that patients in the study are untraceable from the study database. Surgeons that participate in the SPRIMACC study are asked to keep a password coded file that can identify individual patients locked away in their practice.

13.4 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems must be reviewed by the investigator or designee.

13.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

14 PUBLICATION/DATA SHARING POLICY

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

15 LITERATURE REFERENCES

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APPENDICES

APPENDIX A: Schedule of Events
APPENDIX B: Informed consent
APPENDIC C: Case Report Form

APPENDIX A: Schedule of Events

Procedures		Screening (Day –10 to –1)	Study Visit 1 (Day 0)	Study Visit 2 (Day of Discharge)	Study Completion (Day 30 from discharge)	Premature Discontinuation
Signed Consent Form			X			
Assessment of Eligibility Criteria		X	X			
Review of Medical and medication History/functional status			X			
Physical examination		X	X			
Abdomen ultrasound or CT/RMN if necessary		X				
Stratify CBDS risk		X				
Blood test	Blood count	X	X			
	PCR	X	X			
	Liver function test	X	X			
	Urea		X			
	Na/K		X			
	Creatinine		X			
	ABGs		X			
	PT-INR		X			
	PCT		X			
Electrocardiogram			X			
Vitals	Blood pressure		X			

Procedures		Screening (Day –10 to –1)	Study Visit 1 (Day 0)	Study Visit 2 (Day of Discharge)	Study Completion (Day 30 from discharge)	Premature Discontinuation
	Pulse		X			
	Temperature		X			
	Respiratory rate					
Glasgow coma Scale			X			
Calculate Chole-risk score, POSSUM score, mFI, CCI, ASA score and Apache II score			X			
Stratify Cholecystitis severity according to TG 2018			X			
Record intraoperative data				X		X
Record complications according to Clavien-Dindo				X	X	X
Record length of stay				X		X
Record re-admission					X	X

APPENDIX B: Informed Consent

TITLE:

Validation and comparison of Scores for Prediction of RIsk for post-operative major Morbidity after cholecystectomy in Acute Calculous Cholecystitis: protocol for a prospective multicenter observational study (SPRIMACC)

Version n.1 11/4/21

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This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please ask. Take the time to read this carefully and to understand any accompanying information. You will receive a copy of this form for your records.

BACKGROUND
You are being asked to take part in this study because you have been diagnosed with an Acute calculous Cholecystitis (ACC). ACC is the inflammation of the gallbladder due to biliary stones and it is the first clinical presentation in 10-15% of patients with gallstone-related complication. The best treatment for ACC is cholecystectomy, a surgical intervention to remove the gallbladder. For high-risk patients (e.g. patients with many associated pathologies, elderly patients) less invasive treatments have recently been introduced. There are many preoperatory score which

could be used pre-operatively to predict the risk of complicated post-operative course, but none have been definitely validated for cholecystectomy.
A reliable score would predict post-operatory risk of complications and would give to patients and clinicians a useful tool in choosing the best treatment for ACC for each patient.

WHAT IS THE PURPOSE OF THE STUDY?
The purpose of the study is to validated a newly created risk score named “Chole-Risk” and compare its reliability with other existing risk scores.

WHAT WOULD YOU HAVE TO DO?
If you accept to participate to this study you would have to sign this informed consent. You will be subjected to routine blood tests, ABGs, electrocardiogram, abdominal ultrasound and, if necessary, abdominal CT scan or Magnetic Resonance. All these tests would have been carried out for the pathology of which you are affected.
30 days after discharge you will be contacted by phone for a telephone questionnaire about your health.
Data about your exams, you intra-operative and post-operative course will be collected.

WHAT ARE THE RISKS?
There are no additional risks associated with participation in the study. You will be subjected to normal clinical practice treatments for your condition.

DO YOU HAVE TO PARTECIPATE?
You do not have to give permission for you to continue participating in the trial. This will not affect your medical care if you decline to participate further in any way.

WHAT ELSE DOES YOUR PARTICIPATION INVOLVE?
The investigators would like to follow up with you once you have left the hospital to collect specific data regarding your health after discharge. The investigators would like to contact you to conduct a phone interview 30 days after surgical intervention after leaving hospital to assess your overall health. If you consent to continue participating in this study, you may agree to participate in the initial part of the study and decline any further contact or participation at any time.

WILL YOU BE PAID FOR PARTICIPATING, OR DO YOU HAVE TO PAY FOR ANYTHING?
You will neither be paid nor have to pay for participating in this study.

WILL YOUR RECORDS BE KEPT PRIVATE?
By signing this consent form, you authorize (allow) the study doctor and his team to use and release coded and non-personally identifiable information from your Study Records. The information is requested in order to better understand your health history, the treatments (procedures, medications) you received, the outcomes and how those may link to our research findings. Only a limited number of individuals from the research team will have access to your identifying information. Participants will be immediately assigned a unique Study ID and all further communications between team members will only refer to this Study ID. The master list containing the identifying information will be kept in a locked safe not available to or accessible by the research side of the project.

Noting that no identifying data that can be linked to any one patient will ever be released, once the results of this trial are published the group data of the entire study population will be available to the scientific community.
Your authorization to obtain and use your study information has no expiration date. However, you can withdraw (take back) your consent whenever you want. You can do this by giving notice to the Principal Investigator, and we will ask you to send a written request for your records. Any of your stored data would then be destroyed.

SIGNATURES
Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardizing your health care. If you have further questions concerning matters related to this research, please contact:

Dr. Paola Fugazzola
Dr. Lorenzo Cobianchi
Dr. Matteo Tomasoni

Participant's Name	Signature and Date
Investigator/Delegate's Name	Signature and Date

The Ethics Board of IRCCS Ospedale San Matteo has approved this research study.

A signed copy of this consent form has been given to you to keep for your records and reference.

APPENDIX C: CASE REPORT FORM

Patient code:
Institution:
Date of enrolment:
Phone number:

Patient data	Sex	Male [ ] Female [ ]	
	Age	_____	
	Date of symptoms onset	___/___/____	
	Date of admission	___/___/____	
Visit 1 (Day of EC)			
Pre-operative data	Diagnosis of Acute Calculous Cholecystitis according to TG 2018?	Yes [ ] No [ ]	
	Perforated gallbladder?	Yes [ ] No [ ]	
	Israelian Score for CBDS	CBD width by US ≥ 7mm	Yes [ ] No [ ]
		Total bilirubin ≥ 1.8	Yes [ ] No [ ]
		Age ≥70	Yes [ ] No [ ]
		Israelian Score	_____
	Associated CBDS (confirmed by EUS or MRCP)	Yes [ ] No [ ]	
	Pre-operative ERCP?	Yes [ ] No [ ]	
	BMI	_____	
	ACC grade (according to TG 2018)	Hypotension with dopamine >5ug/kg/min or norepinephrine (any dose)	Yes [ ] No [ ]
		Decreased level of consciousness	Yes [ ] No [ ]
		pO2/fiO2<300	Yes [ ] No [ ]
		Oliguria	Yes [ ] No [ ]
		Creatinine>2mg/dl	Yes [ ] No [ ]
		PT-INR>1.5	Yes [ ] No [ ]
		Platelet count <100,000/mm3.	Yes [ ] No [ ]
		WBC>18,000/mm3	Yes [ ] No [ ]
		Palpable tender mass in the right upper abdominal quadrant	Yes [ ] No [ ]

		Duration of complaints >72 h		Yes [ ] No [ ]
		Gangrenous cholecystitis		Yes [ ] No [ ]
		Pericholecystic abscess		Yes [ ] No [ ]
		Hepatic abscess		Yes [ ] No [ ]
		Biliary peritonitis		Yes [ ] No [ ]
		Emphysematous cholecystitis		Yes [ ] No [ ]
		ACC grade		____
Scores for prediction of risk	Chole risk score	previous abdominal interventions?		Yes [ ] No [ ]
		previous percutaneous cholecystostomy?		Yes [ ] No [ ]
		Diabetes?		Yes [ ] No [ ]
		CCI > 6?		Yes [ ] No [ ]
		increased total bilirubin > 2 mg/dL?		Yes [ ] No [ ]
		dilated bile duct?		Yes [ ] No [ ]
		ACC grade (according to TG 2018)		_____
		Chole-risk score:		_____
	POSSUM score	Cardiac sign	Diuretic, digoxine, antianginal or hypertensive therapy	Yes [ ] No [ ]
			Peripheral oedema	Yes [ ] No [ ]
			Warfarin therapy	Yes [ ] No [ ]
			Raised Jugular venous pressure	Yes [ ] No [ ]
		Chest radiography	Borderline cardiomegaly	Yes [ ] No [ ]
			Cardiomegaly	Yes [ ] No [ ]
		Respiratory history	Dyspnoea on exertion	Yes [ ] No [ ]
			Limiting dyspnoea	Yes [ ] No [ ]

			Dyspnoea at rest (rate >30/min)	Yes [ ] No [ ]
		Systolic blood pressure		____mmHg
		Pulse		_____ beats/min
		Glasgow Coma Scale		_____ points
		Haemoglobin		_____g/dL
		White cell count		_____ x10^3/uL
		Urea		_____mg/dL
		Sodium		____ mEq/L
		Potassium		_____mEq/L
		ECG	Atrial fibrillation	Yes [ ] No [ ]
			5 ectopic beats/min or Q waves or St/T wave changes	Yes [ ] No [ ]
			Any other abnormal rhytm	Yes [ ] No [ ]
		Physiological Score		_____
		Operative severity Score		_____
		Total POSSUM		_____
	Modified Frailty Index	patient functional status before surgery partially or totally dependent		Yes [ ] No [ ]
		diabetes mellitus treated with insulin or oral medications		Yes [ ] No [ ]
		hypertension requiring treatment		Yes [ ] No [ ]
		congestive heart failure (CHF)		Yes [ ] No [ ]
		myocardial infarction (MI)		Yes [ ] No [ ]
		prior cardiac surgery or percutaneous coronary angioplasty, or history of angina		Yes [ ] No [ ]
		chronic obstructive pulmonary disease (COPD) or pneumonia		Yes [ ] No [ ]

		rest pain or gangrene secondary to peripheral vascular disease (PVD) or PVD treated with angioplasty, revascularization, amputation	Yes [ ] No [ ]
		impaired sensorium within 48 h prior to the surgical procedure not in the context of concomitant neurologic disease such as dementia	Yes [ ] No [ ]
		history of transient ischemic attack (TIA) or cerebrovascular accident (CVA) without neurologic deficits	Yes [ ] No [ ]
		CVA with neurologic deficits	Yes [ ] No [ ]
		Modified Frailty Index	_____
	Charlson's Comorbidity Index	History of myocardial infarction	Yes [ ] No [ ]
		Congestive heart failure	Yes [ ] No [ ]
		Peripheral vascular disease (includes aortic aneurysm>=6cm)	Yes [ ] No [ ]
		Cerebrovascular disease: accident with mild or no residua o TIA	Yes [ ] No [ ]
		Dementhia	Yes [ ] No [ ]
		Hemiplegia	Yes [ ] No [ ]
		Chronic pulmonary disease	Yes [ ] No [ ]
		Connective tissue disease	Yes [ ] No [ ]
		Peptic ulcer disease	Yes [ ] No [ ]
		Mild liver disease (without portal hypertension, includes chronic hepatitis)	Yes [ ] No [ ]

		Moderate or severe liver disease	Yes [ ] No [ ]
		Diabetes without end-organ damage (excludes diet-controlled alone)	Yes [ ] No [ ]
		Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, brittle diabetes)	Yes [ ] No [ ]
		Moderate or severe renal disease	Yes [ ] No [ ]
		Tumour without metastasis (exclude if >5years from diagnosis)	Yes [ ] No [ ]
		Metastatic solid tumour	Yes [ ] No [ ]
		Leukemia (acute or chronic)	Yes [ ] No [ ]
		Lymphoma	Yes [ ] No [ ]
		AIDS (not just HIV positive)	Yes [ ] No [ ]
		Charlson's Comorbidity Index	_____
	ASA score	_____	
	Apache II	Temperature	_____ °C
		Mean arterial pressure	_____ mmHg
		Heart rate	_____
		Respiratory rate	_____
		FiO2	_____
		A-aDO2	_____
		PaO2	_____mmHg
		Arterial pH	_____
		Serum creatinine	_____ mg/dL
		Hct	_____ %
		immunocompromise	Yes [ ] No [ ]
		Severe organ insufficiency	Yes [ ] No [ ]
		HCO3	_____ mmol/L
		Apache II score	_____
	PCT	_____ ng/mL	

Visit 2 (Day of discharge)			
Intraoperative data	Date of EC	___/___/____	
	Operative time	_____ min	
	Initially laparotomic?	Yes [ ] No [ ]	
	If initially laparoscopic, conversion to open surgery?	Yes [ ] No [ ]	
	Bail out procedure?	Yes [ ] No [ ]	
		If yes, what? _____ _____	
	Intraoperative complication?	Yes [ ] No [ ]	
		If yes, what? _____ _____	
	Intraoperative death	Yes [ ] No [ ]	
Post-operative in-hospital data	Post-operative in-hospital complications?	Yes [ ] No [ ]	
		If yes, what? _____	
		Report Clavien-Dindo Grade of each complication:	_____ _____ _____ _____
	Length of stay	_____ days	
Study completion (Day 30 ± 7)			
Follow-up data	Post-operative post-discharge 30-day complications?	Yes [ ] No [ ]	
		If yes, what? _____	

		Report Clavien-Dindo Grade of each complication:	_____ _____ _____ _____
	Readmission within 30 days from discharge?	Yes [ ] No [ ]	
		If yes date of readmission: If yes, why? _____ _____	