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Keywords: Acute cholecystitis; cholecystectomy; surgery; timing; complication; mortality.

Article

Timing of Early Cholecystectomy: A Multicentric Prospective Observational Study

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Abstract: The definition of Early Cholecystectomy (EC) is still debatable. This paper aims to find whether the timing of EC affects outcomes. This is a multicentric prospective observational study including patients with acute calculous cholecystitis (ACC) who had cholecystectomy within ten days from the onset of symptoms. Kruskall-Wallis test, Fisher's Exact test and Spearman rank correlation were used for statistical analysis. The patients were divided into three groups depending on the timing of the operation: 0-3 days, 4-7 days, or 8-10 days from the onset of symptoms. 1117 patients were studied over a year. The time from the onset of symptoms to EC did not affect the postoperative complications and mortality, the conversion and the reintervention rate. It was a significant risk factor for intraoperative complications (0-3 days, 2.8%; 4-7 days, 5.6%; 8-10 days, 7.9%; p=0.01) and subtotal cholecystectomies (0-3 days, 2.7%; 4-7 days, 5.6%; 8-10 days, 10.9%; p<0.001). ACC is an evolutive inflammatory process and, as the days go by, the local and systemic inflammation increases which makes surgery more complex and difficult with higher risk of intraoperative complications. We recommend performing EC for ACC as soon as possible within the first ten days of the onset of symptoms.

Keywords: acute cholecystitis; cholecystectomy; surgery; timing; complication; mortality

1. Introduction

Early cholecystectomy (EC) represents the gold standard for treating acute calculous cholecystitis (ACC) [1,2]. It is superior to both intermediate cholecystectomy (performed between 7 days and 6 weeks of hospital admission) and delayed cholecystectomy (performed between 6 weeks and 3 months from hospital admission) [1]. EC has shorter total hospital stay and lower cost, but longer operative time [3,4].

However, the definition of EC is still debatable without available definitive data. The World Society of Emergency Surgery (WSES) guidelines defined "early cholecystectomy" when performed within 7 days of hospital admission and within 10 days of the onset of symptoms [1]. The Japanese guidelines defined EC when performed as soon as possible, preferably within 72 hours from the onset of symptoms, but even after this time [2].

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Multiple studies and meta-analyses comparing different timing of EC revealed no significant association between timing of operation and postoperative mortality or morbidity [4–7], but longer post-operative LOS in the group of patients with longer times from admission to surgery [5,8]. On the other hand, a large retrospective observational study [9] including 43870 patients in England who underwent emergency cholecystectomy on index admission showed a significantly lower biliary complication rate in patients undergoing cholecystectomy within 3 days of admission. Another retrospective study [10] including 34151 cholecystectomies for ACC showed that operations performed on hospital days 3-7 had increased 30-day mortality and morbidity in comparison to hospital day 1 or hospital day 2. On multivariable analysis, the number of days from admission to EC was an independent predictor of mortality.

Focusing on the conversion rate, some observational studies [5] showed that patients who underwent operation later in the course of admission were more likely to require an open procedure. Other studies [8,11] did not find difference in the conversion rate, but an increasing rate of difficult surgical procedures and an increasing operative time. A recent meta-analysis has found that cholecystectomy which was performed within 24 h of admission has not reduced the post-operative complications [7], but has reduced LOS. Many of these studies are not comparable because they consider different time intervals. A recent meta-analysis has shown that cholecystectomies performed within 72 h of symptoms have reduced conversion rate and LOS in comparison to cholecystectomy ≤7 days [4,7]. No differences in complication rate and bile duct injuries have been found [4]. There are three RCTs [12–14] and other prospective non-randomized studies [6,11] which compare different timings of EC from the onset of symptoms. Three RCTs randomized patients with ACC to receive EC within 72 hours or after 4-7 days from the onset of symptoms. In these studies no differences in postoperative complication rate and conversion rate were found, but patients who received EC within 72 hours had significantly shorter postoperative LOS. In the studies by Chandler et al. [12] and by Onuk et al. [13] there was no difference in the duration of the surgery, while in the study by Jan et al. [14] the operative time was longer in patients who were operated on after 72h. Furthermore, Jan et al. [14] did not find significant difference in intraoperative complications, while Chandler et al. [12] found significantly greater blood loss in those operated on after 72h. However, none of the RCTs and the prospective non-randomized studies had enough powered sample size. The only study that reported data about sample size calculation [13], had a power of 34%. A Cochrane systematic review [15] highlighted the difficulty of obtaining sufficient data on this topic through RCTs because studies with enough power would involve thousands of patients.

Accordingly, there is lack of high-quality and properly powered studies that stratify the intra and post-operative risks of EC based on the delay of surgery from the onset of symptoms, especially when considering an inclusive time of 10 days from the onset of symptoms. The validation and comparison of Scores for Prediction of Risk for post-operative major Morbidity after cholecystectomy in Acute Calculous Cholecystitis (S.P.Ri.M.A.C.C.) study was conceived as a WSES prospective multicentre observational study on patients with ACC who are candidates for EC aiming to validate different scores in predicting postoperative complications [16]. This current paper is a posthoc analysis of the S.P.Ri.M.A.C.C study aiming to define the effects of different timings of EC (within 10 days from the onset of symptoms) on intra and postoperative outcomes.

2. Materials and Methods

2.1. Ethical considerations

The medical ethics board of the trial coordinating centre IRCCS San Matteo Hospital, Pavia, Italy, approved the S.P.Ri.M.A.C.C. study protocol. All regional ethics committees of the participating centres provided secondary approval. Before enrollment, patients provided both verbal and written informed consent. The S.P.Ri.M.A.C.C. trial was carried out in line with the Helsinki Declaration.

2.2. Design

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The S.P.Ri.M.A.C.C. study is an observational multicenter prospective study endorsed by the WSES. 1253 patients from 79 locations in 19 nations were enrolled between September 1, 2021, and September 1, 2022. The study was listed in LegalTrial.gov under case number NCT04995380. 1117 participants were included in the study after patients with incomplete information regarding the timing of EC were excluded. Within 10 days after the onset of symptoms, EC was administered to all patients. The goal of the study was to determine whether there was a statistically significant difference in the rate of intraoperative complications between individuals who underwent surgery at various times after the onset of their symptoms (0-3 days, 4-7 days, 8-10 days).

2.3. Studied variables

The intraoperative complication rate was the primary objective. It included haemorrhage above 500 mL, biliary tree injuries, bowel perforation, major vascular injuries, general anaesthetic respiratory complications, and general anaesthesia cardiac issues. The secondary endpoints were represented by the rate of conversion from laparoscopic to laparotomy, the rate of needing bailout procedures (subtotal cholecystectomy, fundus-first cholecystectomy, laparoscopic drainage only), the operative time, the in-hospital postoperative major complications (defined as complications with Common Terminology Criteria for Adverse Event, CTCAE 3), the 30-day postoperative major complications (CTCAE 3), the post-operative length of stay (LOS), the in-hospital mortality, and the 30-day mortality.

2.4. Inclusion and exclusion criteria

The following criteria had to be met for a patient to be included: 1) have a diagnosis of ACC according to the 2018 Tokyo Guidelines; 2) be a candidate for EC during the index admission; 3) be older than 18 years of age; 4) be stratified for the risk of common bile duct stones and, in case of confirmation, receive preoperative ERCP 5) sign a written informed consent form, inclusive of the date and 6) be willing to comply with all study protocol rules and be available for the duration of the investigation.

Pregnancy or lactation, acute cholecystitis unrelated to a gallstone cause, symptoms appearing more than 10 days before cholecystectomy, concurrent cholangitis or pancreatitis, intraoperative treatment of common bile duct stones, or anything else that would prevent full compliance with or completion of the study were the exclusion criteria.

2.5. Statistical analysis

Sample size: for the sample size calculation, the investigators grounded on the RCT by Jan et al. (14) in which patients with ACC were randomized to receive EC within 72h from the onset of symptoms (group 1) or after 72h up to 7 days from the onset of symptoms (group 2). In the study, the intraoperative complication rate in group 1 was 2%, while in group 2 was 6%. 1,000 patients are required to have a 90% chance of detecting, as significant at the 5% level, an increase in the primary outcome measure. The patients were divided into three different groups depending on the time from onset of symptoms: group I from 0-3 days, Group II from 4-7 days, and Group III from 8-10 days.

Variables comparison: The three groups were compared using the Kruskall-Wallis test for continuous or ordinal data and Fisher's Exact test for categorical data. Spearman rank correlation was used to study the correlation between the continuous or ordinal data. A P value of less than 0.05 was accepted as significant. SPSS version 26 was used for comparison.

3. Results

58.7% of patients received EC within 3 days, 32.2% from 4 to 7 days and 9.0% from 8 to 10 days from the onset of symptoms. The mean age was 59 and the mean POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) Physiological score (PS) was 20.7. The intraoperative complication rate was 4.1%. The most frequent complication was intraoperative bleeding >500ml (16 patients). Other intraoperative complications were biliary tree

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injuries (8 patients), bowel perforation (1 patient), respiratory complications (3 patients), cardiac complications (3 patients) and others (16 patients). 8.4% of patients needed a bail-out procedure (49 subtotal cholecystectomies, 65 patients treated with a fundus-first technique and 1 patient received only laparoscopic drainage). Preoperative characteristics of the three groups of patients are reported in Table 1. Patients were similar in terms of age and BMI. Patients operated after 8-10 days from the onset had a significantly higher POSSUM PS (median (IQR): 0-3 days, 19 (15-24); 4-7 days, 19 (16-24); 8-10 days, 21 (17-26); p=0.012). Patients operated on within 3 days from onset of symptoms had lower ACC severity grades (mean (SD): 1.6 (0.5) for 0-3 days, 1.8 (0.4) for 4-7 days, 1.7 (0.5) for 8-10 days; p=0.012).

Table 1. Preoperative characteristics of the patients who were operated on for acute cholecystitis from September 2021 to September 2022 from 79 centres in 19 countries by the time between the onset of symptoms and surgery, n=117.

Variables	Onset of Symptoms			P value
	0-3 days n=656	4-7 days n=360	8-10 days n=101	
Age (years)	59 (46-72)	62 (50-74)	61 (46-74)	0.14
BMI	26.7 (24.3-29.4)	26.7 (24.2-29.4)	26.3 (23.6-28.9)	0.4
ACC severity grade	2 (1-2)*	2 (2-2)*	2 (1-2)*	<0.001
POSSUM physiological score	19 (15-24)	19 (16-24)	21(17-26)	0.012
Days from admission to surgery	1 (0-1)	2 (0-3)	6 (2-8)	<0.001

BMI: Body Mass Index, ACC: Acure Cholecystitis, POSSUM: Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity, PS: physiological score. Data are presented as median (IQR). P value Kruskall Wallis test. * mean (SD) of ACC severity grade: 1.6 (0.5) for 0-3 days, 1.8 (0.4) for 4-7 days, 1.7 (0.5) for 8-10 days.

Table 2 shows intraoperative outcomes. A higher number of days from the onset of symptoms to EC was a significant risk factor for longer operative times (median (IQR): 0-3 days, 90 (60-120) minutes; 4-7 days, 100 (65-134.5) minutes; 8-10 days, 107 (74-145) minutes; p<0.001), for needing of bail-out procedures (0-3 days, 6.9%; 4-7 days, 9.7%; 8-10 days, 13.9%; p=0.037) and for intraoperative complications (0-3 days, 2.8%; 4-7 days, 5.6%; 8-10 days, 7.9%; p=0.01). Analyzing the kind of bail-out procedures, the rate of subtotal cholecystectomies significantly increased with the increase of days from onset (0-3 days, 2.7%; 4-7 days, 5.6%; 8-10 days, 10.9%; p<0.001). Figure 1 shows the box-and-whisker plot of the operative time by the time between the onset of symptoms and surgery. The time interval from the onset to EC did not affect the conversion rate to open surgery.

Table 2. Intraoperative outcome of the patients who were operated on for acute cholecystitis from September 2021 to September 2022 from 79 centres in 19 countries by the time between the onset of symptoms and surgery, n=117.

Variables	Onset of Symptoms			P value
	0-3 days n=656	4-7 days n=360	8-10 days n=101	
Operative time (minutes)	90 (60-120)	100 (65-134.5)	107 (74-145)	<0.001
Conversion to open surgery	48 (7.9%)	32 (9.9%)	9 (9.5%)	0.54
Bail-out procedure:	45 (6.9%)	35 (9.7%)	14 (13.9%)	0.037
Subtotal cholecystectomy	18 (2.7%)	20 (5.6%)	11 (10.9%)	<0.001
Fundus-first technique	34 (5.2%)	24 (6.7%)	7 (6.9%)	0.52
Drainage only	1 (0.2%)	0 (0.0%)	0 (0%)	0.99
Intraoperative complications	18 (2.8%)	20 (5.6%)	8 (7.9%)	0.01

Data are presented as median (IQR) or number (%). Percentages were calculated from valid available data. P value Kruskall Wallis test of Fisher's Exact test as appropriate.

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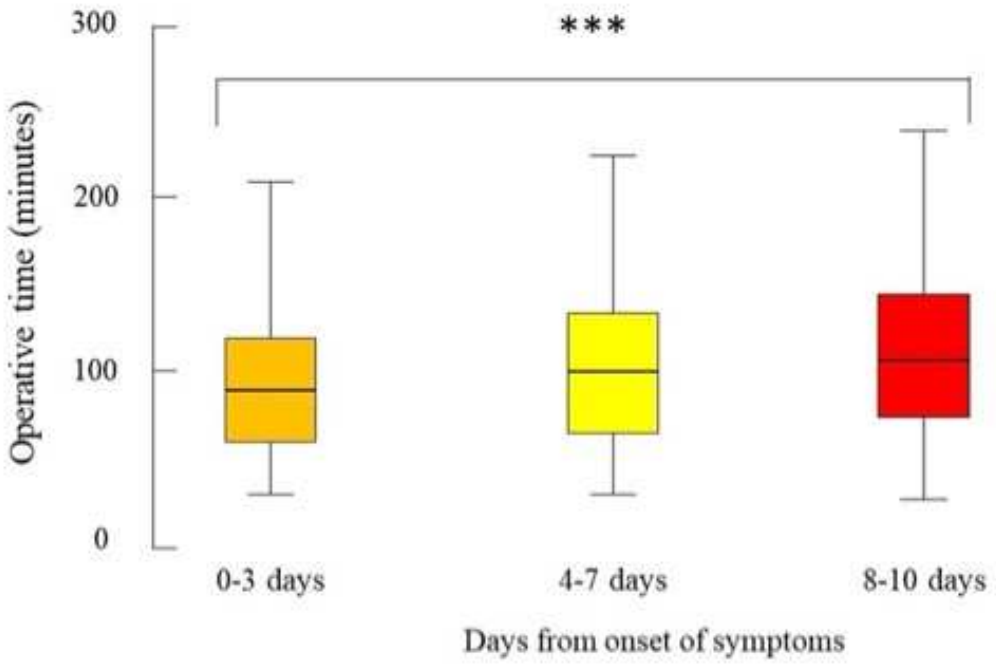

Figure 1. Box-and-whisker plot of the operative time for the patients who were operated on for acute cholecystitis from September 2021 to September 2022 from 79 centres in 19 countries by the time between the onset of symptoms and surgery, n=117. The box represents the 25th to the 75th percentile IQR. The horizontal line within each box represents the median. ***p < 0.001, Kruskal-Wallis test.

Table 3 shows postoperative outcomes. A higher number of days from the onset of symptoms to EC was a significant risk factor for a longer LOS (median (IQR) LOS: 0-3 days, 3 (2-5) days; 4-7 days, 5 (3-7) days; 8-10 days, 8 (3-11) days; p<0.001; patients with a LOS longer than 10 days: 0-3 days, 6.67%; 4-7 days, 10.6%; 8-10 days, 24.8%; p<0.001) (Figure 2). The time from the onset to EC did not affect the reintervention rate, the postoperative complications and mortality.

Table 3. Postoperative outcomes of the patients who were operated on for acute cholecystitis from September 2021 to September 2022 from 79 centres in 19 countries by the time between the onset of symptoms and surgery, n=117.

Variables	Onset of Symptoms			P value
	0-3 days n=656	4-7 days n=360	8-10 days n=101	
Reintervention	16 (2.4%)	6 (1.7%)	0 (0%)	0.29
Inhospital major complication	38 (5.8%)	15 (4.2%)	6 (5.9%)	0.49
30-day major complications	48 (7.3%)	22 (6.2%)	7 (7.1%)	0.78
Inhospital mortality	5 (0.8%)	5 (1.4%)	1 (1%)	0.52
30-day mortality	5 (0.8%)	7 (1.9%)	1 (1%)	0.25
LOS>10 days	43 (6.6%)	38 (10.6%)	25 (24.8)	<0.001
LOS (days)	3 (2-5)	5 (3-7)	8 (3-11)	<0.001

LOS: length of stay. Data are presented as median (IQR) or number (%). P value Kruskall Wallis test of Fisher's Exact test as appropriate.

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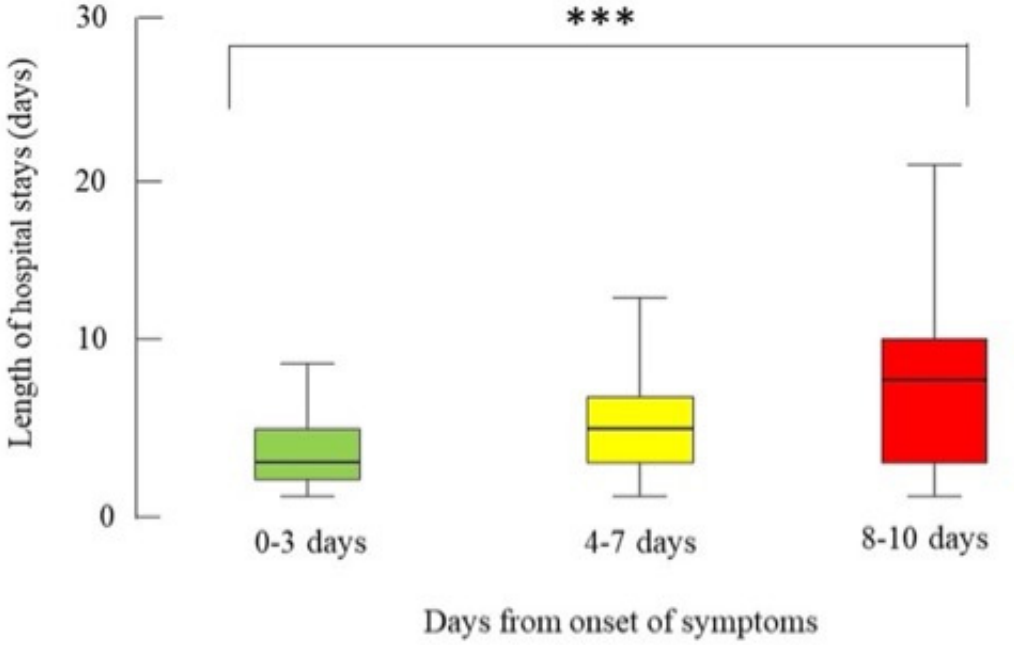

Figure 2. Box-and-whisker plot of the length of hospital stay (days) of the patients who were operated on for acute cholecystitis from September 2021 to September 2022 from 79 centres in 19 countries by the time between the onset of symptoms and surgery, n=117. The box represents the 25th to the 75th percentile IQR. The horizontal line within each box represents the median. ***p < 0.001, Kruskal-Wallis test.

There was a statistically significant, small positive correlation between days from onset of symptoms and LOS (r=0.26, p<0.001), POSSUM PS (r= 0.01, p<0.001) and operative time (r=0.14, p<0.001) (Table 4).

Table 4. Correlations between different continuous and ordinal data of the patients who were operated on for acute cholecystitis from September 2021 to September 2022 from 79 centres in 19 countries by the time between the onset of symptoms and surgery, n=117.

		Length of stay	Days from admission to EC	POSSUM PS	Operative time
Days from onset to EC	**Correlation**	0.26	0.53	0.01	0.14
	P value	<.001	<.001	0.002	<.001
Length of stay	**Correlation**	-------	0.35	0.31	0.33
	P value	-------	<.001	<.001	<.001
Days from admission	**Correlation**	-------	-------	0.06	.167
	P value	-------	-------	0.049	<.001
POSSUM score	**Correlation**	-------	-------	-------	0.16
	P value	-------	-------	-------	<.001

EC: early cholecystectomy, POSSUM: Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity, PS: physiological score. P value= Pearson rank correlation.

4. Discussion

The present study is the first prospective study of our knowledge focusing on the ideal timing of EC with a sample size calculated on a high study power. These data showed that the risk of intraoperative complications, the risk of needing a bail-out procedure (e.g., subtotal cholecystectomy), the operative time and, to a lesser degree, the LOS increase for each time interval (0-3 days, 4-7 days, 8-10 days) from the onset of symptoms to EC. The evolution of the inflammatory

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process, with the passage of days, makes it more difficult to dissect tissues, recognize structures and increases the tendency to bleed. The ACC severity grade and the POSSUM PS rise with the passing of days, due to the exacerbation of the local and systemic inflammation. Despite the greater difficulty of the intervention, the delay in performing EC, if within 10 days from the onset of symptoms, did not affect post-operative complications, postoperative mortality, risk of conversion to open surgery and need for reintervention.

The definition of EC in terms of timing is still debatable [4–11]. Most of the existing studies are unpowered or they are not comparable because they consider different timing definitions. Some consider the time interval from the onset of symptoms while others from hospitalization. Patients can go to the emergency department after very different intervals of time from the onset of symptoms, and then at different stages of the disease. This may depend on age, comorbidities, geographic location, pain tolerance and social class. This can lead to poor population uniformity when the timing is based on the time of admission. Basing the timing on the onset of symptoms allows to create more homogeneous patient groups for the stage of disease and the surgical risk.

Compared with other surgical urgencies, physicians often procrastinate cholecystectomy for ACC. Hospitals and community care often fail to ensure patients with ACC an ideal timing for surgery. General practitioners, emergency doctors and surgeons often try to treat ACC medically before considering surgery. This, combined with the organizational issues of operating rooms, increases the time between the onset of symptoms and EC. It worsens the general and local inflammatory condition, increases the surgical complexity and rises the risk of intraoperative complications.

The time between the onset of symptoms and the presentation of the patient in the emergency department does not depend on the physician. However, the physician, considering the organizational issues within the health care system and availability of the operating rooms, should do everything possible to ensure a patient with ACC has a cholecystectomy performed as early as possible.

Probably a proper surgeon-patient and surgeon-general practitioner knowledge translation could shorten the time between the onset of symptoms and emergency department presentation. Surgeons should recommend symptomatic patients with cholelithiasis during outpatient visits to go to the hospital as soon as possible. Furthermore, the time between the arrival in the emergency room and the surgical visit should be optimized. Clinical examination, blood tests and ultrasound are usually sufficient to diagnose ACC. Emergency doctors should not delay the management by performing uneeded examinations or attempts for medical therapy when there is clear indication for surgery.

Main bile duct stones associated with ACC often delay EC because of the need for MRCP or ERCP to have a clear management plan. Probably, a single-stage intraoperative ERCP or a laparoscopic cholangioscopy combined with laparoscopic cholecystectomy will reduce the time for EC [17].

Our study has some limitations. It is a non-randomized study with possible confounding factors. However, given the large sample size required, it would be difficult to carry out a RCT on this topic. Furthermore, we were interested in the generalizability of the study which will contain more heterogeinity in the data. This included some developing countries with lack of training in research methodology including performing RCTs. To our knowledge, the prospective nature and the large sample size of our study, despite being type II research data, provide the highest quality data available in the literature. An adequate RCT would be possible only through a multicenter study with a high degree of organization and international cooperation.

5. Conclusions

In conclusion, considering that EC is superior to delayed and interval cholecystectomy [1,3,4], this study clarifies the best timing of EC. Our study has shown that delaying EC up to ten days from the onset of symptoms does not affect postoperative complications and mortality. However, ACC is an evolutive inflammatory process and, as the days go by, the local and systemic inflammation

increases which makes surgery more complex and difficult with higher risk of intraoperative complications. We recommend performing EC for ACC as soon as possible within the first ten days of the onset of symptoms6.

Author Contributions: LA: PF: study conception; PF, LA, LC, FDM, FMAZ, MC: manuscript conception and draft and contribute to important scientific knowledge; FMAZ statistical analysis of the data. PF, LC, FDM, FMAZ, MT, MC, FC, TD, CNF, SF, VM, BS, JV, FC, LA gave substantial contributions to the interpretation of data for the work and critically revised the manuscript; PF, MT and S.P.Ri.M.A.C.C. Collaborative Group: substantial contributions to the acquisition of data and draft critically revised. All authors gave the final approval and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by Medical Ethics Board of the trial coordinating centre IRCCS San Matteo Hospital, Pavia, Italy (protocol code P20210050641, date of approval 04/06/2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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