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original article

Impact of cardiovascular/diabetic comorbidity on conversion rate during laparoscopic cholecystectomy for acute cholecystitis: a multi-center study on early *versus* very delayed approach

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SUMMARY: **Impact of cardiovascular/diabetic comorbidity on conversion rate during laparoscopic cholecystectomy for acute cholecystitis: a multi-center study on early *versus* very delayed approach.**

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Background. *The impact of diabetes and cardiovascular comorbidity on laparoscopic cholecystectomy has been long debated, evaluating them as risk factors for conversion to an open procedure especially in patients with acute cholecystitis: an "early" procedure, as suggested by 2013 Tokyo guidelines, has been compared to a "very delayed" one in patients under anticoagulant/antiplatelet therapy or treated for diabetes and referred by medical wards to surgery after the acute period.*

Methods. *We selected 240 patients operated for acute cholecystitis by laparoscopy over the last 4 years at St. Orsola University Hospital-Bologna and Umberto I University Hospital-Rome, comparing 98 diabetic/cardiovascular patients* versus *142 subjects as control group: the selection was based on operative timing, "early" (73 patients treated within 3 days) and "very delayed" (167 patients operated after 6 weeks).*

Results. *In the "early" subgroup there was no difference comparing diabetic/cardiovascular patients (31 pts)* versus *control group (42 pts) while in the "very delayed" subgroup among diabetic/cardiovascular patients (67 pts) there was significantly male predominance, ASA III/IV prevalence and less positive imaging findings* versus *control group (100 pts). In both subgroups, the conversion rate was significantly higher for diabetic/cardiovascular patients ("early"=25.8% and "very delayed"=8.95%) compared to control groups ("early"=4.76% and "very delayed"=1%), showing a trend (p=0.058) towards an increased conversion rate in the early approach among diabetic/cardiovascular group.*

Conclusions. *Our study showed a significantly increased conversion rate to an open cholecystectomy for diabetic/cardiovascular patients affected by cholecystitis, especially within 3 days by the acute episode.*

KEY WORDS: Diabetes - Cardiovascular comorbidity - Acute cholecystitis - Laparoscopy - Conversion rate - Timing.

Introduction

Even though laparoscopic cholecystectomy for acute cholecystitis is one of the most commonly performed operations by general surgeons, current practices remain varied despite growing evidence in the literature defining best method. Although acute cholecystitis has previously been considered a relative contraindication for laparoscopic cholecystectomy (1), recent research has provided evidence that it can be safely performed in such cases: in fact, the 2013 Tokyo guidelines for the diagnosis and management of acute cholecystitis (2) recommend laparoscopy for Grade I acute cholecystitis (3, 4). However, in some cases the technical difficulties of the laparoscopic procedure can make unavoidable the conversion to open cholecystectomy: it has been reported that 1.8-27.7% of laparoscopic cholecystectomies are converted to open surgery during the

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operation (5). Diabetes has been historically considered a risk factor for the development of acute cholecystitis (6, 7), especially in form of gangrenous cholecystitis (8), subsequently increasing the risk of conversion from a laparoscopy to an open procedure (9-21): there has been debate if in such cases the laparoscopic procedure must be performed at all (22-26) and, when feasible, the timing of it (27). In parallel, a long-standing issue (28) has been quarreled over the last 30 years upon the coagulative profile (29) and subsequent feasibility (30-35) of laparoscopic cholecystectomy among cardiovascular patients, prone to intraoperative bleeding especially if under anticoagulant/antiplatelet therapy. Tokyo guidelines (2) have remarked the need to operate laparoscopically as soon as possible patients affected by acute cholecystitis in order to reduce the rate of morbidity and mortality, typically within 3 days ("early" approach) from acute episode, but the relationship with some preoperative risk factors for conversion (such as diabetes or cardiovascular morbidity) has not been completely clarified. On the other hand, in clinical practice most of the patients affected by an acute episode of cholecystitis are initially treated by antibiotic therapy in medical wards, and only few weeks later referred for surgery. We performed a retrospective cohort study, registered in a validated common database shared by two Italian institutions (Surgical Emergency Unit at St. Orsola University Hospital-Bologna and Department of Surgical Sciences at "Umberto I" University Hospital-Rome): our purpose was to help clarify this topic, especially aiming to highlight the difference of an "early" (within 3 days) *versus* a "very delayed" (after 6 weeks) operative laparoscopic approach in terms of conversion rate among diabetic/cardiovascular patients affected by acute cholecystitis.

Methods

We performed 983 cholecystectomies over the last 4 years at Surgical Emergency Unit of St. Orsola University Hospital-Bologna and Department of Surgical Sciences of "Umberto I" University Hospital-Rome, sharing all the data in a common database: among these data we excluded from our analysis the cholecystectomies not performed for acute episode, the open cholecystectomies and patients treated by cholecystostomy tubes or any other radiological intervention. Among the remaining 406 laparoscopic cholecystectomies for acute cholecystitis, we performed a further selection of 240 patients (98 diabetic/cardiovascular and 142 subjects as control group) based on operative timing: an "early" subgroup represented by 73 patients treated laparoscopically within 3 days and a "very delayed" subgroup represented by 167 patients operated by laparoscopy after 6 weeks because of late referral by medical wards after successful antibiotic therapy (Figure 1). Moreover, as a monitoring group we reviewed the data of a "not early" subgroup represented by all 333 patients operated laparoscopically after 3 days from the acute episode (150 diabetic/cardiovascular patients *versus* 183 as control group) referred to us by medical wards under or after antibiotic treatment (Figure 2). Among the 3 subgroups "early" (operated laparoscopically within 3 days =73 patients), "not early" (operated laparoscopically after 3 days= 333 patients) and "very delayed" (operated laparoscopically after 6 weeks =167 patients), we analyzed age, gender, ASA score, clinical signs, imaging findings, complications (as defined by the Clavien-Dindo classification) (36), mortality, operative time, conversion rate and post-operative length of stay. Diabetes was defined as a disease in which the body's ability to produce or respond to the hormone insulin is impaired resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood, while cardiovascular co-morbidity was defined by the presence of a group of disorders affecting the heart and blood vessels. The selection for an "early" (within 3 days), "not early" (after 3 days) or "very delayed" (after 6 weeks) treatment was based upon the time of admission in our surgical units: the "not early" or "very delayed" subgroups of patients were initially admitted in medical wards where they were managed successfully or unsuccessfully by antibiotics, and only later, after the conservative therapy ,transferred to our units for surgery. Intra-operatively, the decision to convert was always based upon surgeon's experience (all physicians participating at the study were Attending Surgeons fully trained in laparoscopy). Statistical analysis was performed using one-way analysis of variance, Fisher's exact test and χ^2 test. Categorical variables were described

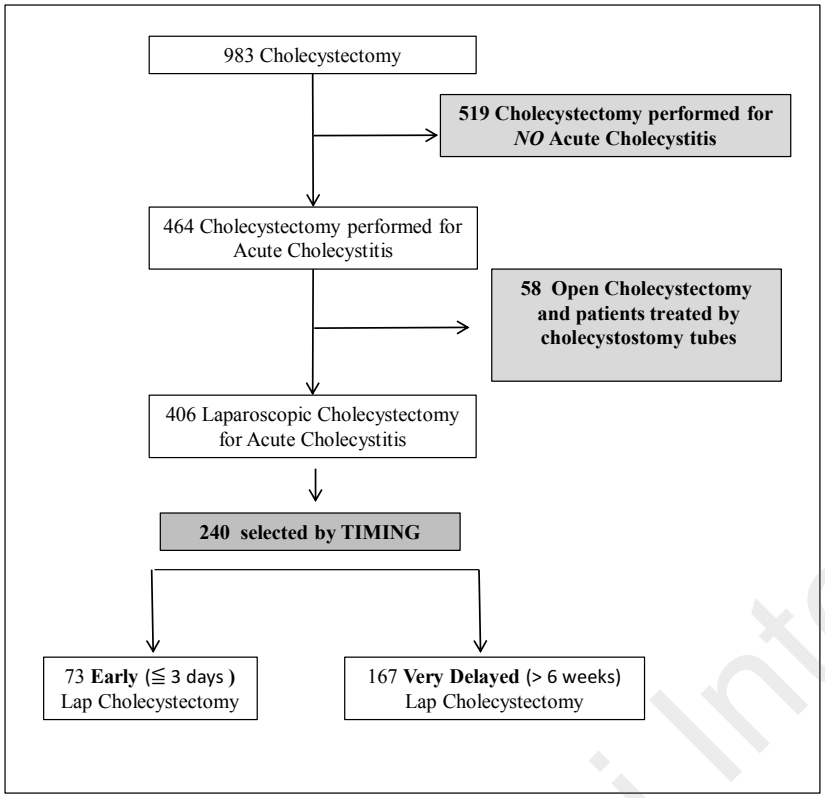

Figure 1 - Flow diagram of "early" and "very delayed" laparoscopic cholecystectomies.

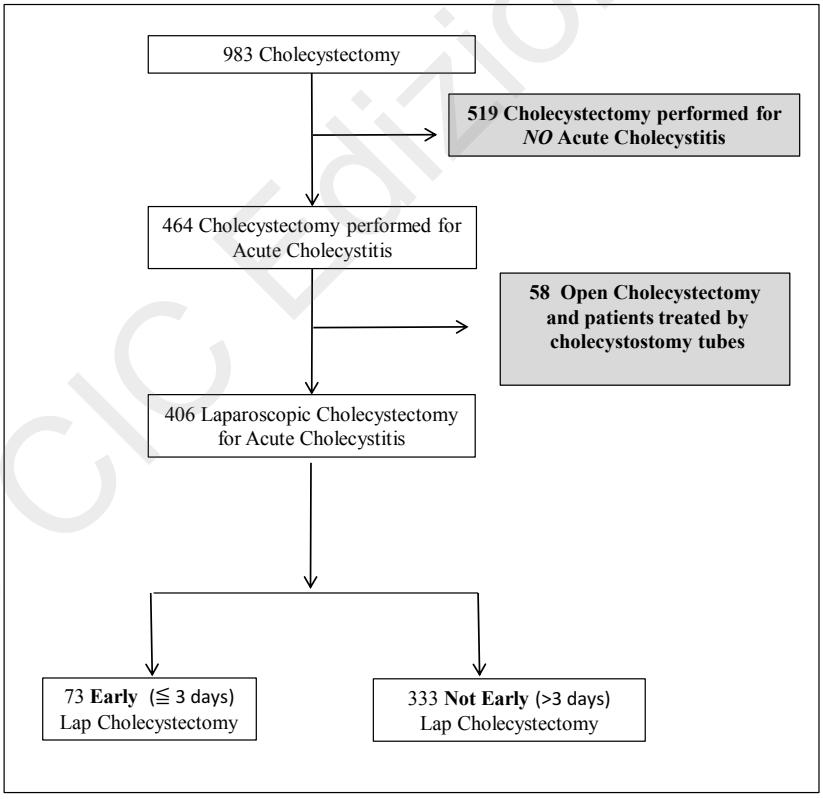

Figure 2 - Flow diagram of "early" and "not early" laparoscopic cholecystectomies.

as numbers, and continuous variables were described as median and ranges. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 13.0 (Chicago).

Results

Our results showed that in the "early" subgroup (Table 1) there was no difference comparing diabetic/cardiovascular patients (31 patients) *versus* control group (42 patients) in terms of age, gender, ASA score, clinical signs, imaging findings, complications and mortality, while in the "very delayed" subgroup (Table 2) among diabetic/cardiovascular subjects (67 patients) there was significantly male predominance, ASA III/IV prevalence and less positive imaging findings *versus* control group (100 patients). In both "early" and "very delayed" subgroups (Tables 3, 4), operative time and post-operative length of stay were not different while the conversion rate to an open cholecystectomy was significantly higher for diabetic/cardiovascular patients ("early"=25.8% and "very delayed"=8.95%) compared to control groups ("early"=4.76% and "very delayed"=1%), showing moreover a trend (p=0.058) towards an increased conversion rate in the "early" subgroup among diabetic/cardiovascular patients (Table 5) when compared to the "very delayed" subgroup. Analyzing the data of the "not early" subgroup (333 patients operated after 3 days) as a monitoring group, even in this case among diabetic/cardiovascular patients there was significantly male pre-

TABLE 1 - SUBGROUP OF PATIENTS OPERATED WITHIN 3 DAYS (EARLY LAPAROSCOPIC CHOLECYSTECTOMY).

	No CV-DM comorbidity	CV-DM comorbidity	p-Value
Number of patients	42	31	-
Age (years)	51,4+15,3	67,3+14,6	0,4680
Male gender	17 (40%)	16 (52%)	0,4758
ASA score I/II and **III/IV**	34/8	21/10	0,2727
Positive clinical signs	29,0 (68%)	27 (88%)	0,0952
Positive imaging findings	37 (88%)	27 (87%)	1,0000
Complications	1/0	1/2	1,0000
(Clavien-Dindo I/II and **III/IV)**			
Mortality	0	2 (6%)	0,1769

CV= cardiovascular; DM= diabetic

TABLE 2 - SUBGROUP OF PATIENTS OPERATED ABOVE 6 WEEKS (VERY DELAYED LAPAROSCOPIC CHOLECYSTECTOMY).

	No CV-DM comorbidity	CV-DM comorbidity	p-Value
Number of patients	100	67	-
Age (years)	46,3+13,4	66,4+12,4	0,2984
Male gender	32 (32%)	40 (59,70%)	**0,0005**
ASA score I/II and **III/IV**	97/3	46/21	**0,0001**
Positive clinical signs	33 (33%)	21 (31%)	0,8671
Positive imaging findings	76 (76%)	32 (47,76%)	**0,0003**
Complications	2/0	5/2	1,000
(Clavien-Dindo I/II and **III/IV)**			
Mortality	0	0	1,000

CV= cardiovascular; DM= diabetic

TABLE 3 - SUBGROUP OF PATIENTS OPERATED WITHIN 3 DAYS (EARLY LAPAROSCOPIC CHOLECYSTECTOMY).

	No CV-DM comorbidity	CV-DM comorbidity	p-Value
Number of patients	42	31	-
Operative time (minutes)	72,8+32,1	104,0+42,9	0,5540
Conversion rate	2/42 (**4,76%**)	8/31 (**25,8%**)	**0,0147**
Post-operative Length of Stay (days)	3,7+2,9	6,3+9,5	0,7689

CV= cardiovascular; DM= diabetic

TABLE 4 - SUBGROUP OF PATIENTS OPERATED ABOVE 6 WEEKS (VERY DELAYED LAPAROSCOPIC CHOLECYSTECTOMY).

	No CV-DM comorbidity	CV-DM comorbidity	p-Value
Number of patients	100	67	-
Operative time (minutes)	70,7+33,5	82,8+35,3	0,8095
Conversion rate	1/100 (**1%**)	6/67 (**8,95%**)	**0,0171**
Post-operative Length of Stay (days)	2,6+1,7	3,9+6,4	0,8176

CV= cardiovascular; DM= diabetic

TABLE 5 - PATIENTS AFFECTED BY CARDIOVASCULAR-DIABETIC COMORBIDITY.

	EARLY LAPAROSCOPIC CHOLECYSTECTOMY (≦ 3 days)	very DELAYED LAPAPAROSCOPIC CHOLECYSTECTOMY (> 6 weeks)	p-Value
Conversion rate	8/31 (**25,8%**)	6/67 (**8,95%**)	0,0584

dominance, ASA III/IV prevalence and less positive imaging findings (and more positive clinical signs) *versus* control group, with a conversion rate significantly higher among subjects affected by diabetes and cardiovascular comorbidity (Tables 6, 7): comparing the "early" *versus* the "not early" subgroup among diabetic/cardiovascular patients, the conversion rate to an open cholecystectomy was not statistically different (Table 8). Table 9 and Table 10 show the univariate and multivariate analysis of 240 laparoscopic "early" and "very delayed" patients (converted and not converted cases), assessing factors associated with conversion.

Discussion

Overall conversion rates of 2-28% from a laparoscopic to an open cholecystectomy have been previously reported in international literature (5), with an increased rate of 6-35% specifically in patients with acute cholecystitis (1). Because conversion from a laparoscopic approach lengthens the procedure and hospital stay, and moreover it is associated with increased morbidity (1), there has been always clinical interest in identifying preoperative risk factors for conversion. Diabetes has been historically considered a risk factor for conversion with a number of published papers related to this issue (9-21): an early prophylactic cholecystectomy in asymptomatic diabetic patients has been recommended before an acute episode of gangrenous cholecystitis develops (often reported in such patients) (8), based on the high incidence of postoperative complications and the increased mortality rates among diabetic patients with acute cholecystitis (37). Another risk factor for conversion has been represented in international literature by the cardiovascular patient: previously, it was thought that laparoscopic cholecystectomy was hazardous in patients receiving oral anticoagulants.

TABLE 6 - SUBGROUP OF PATIENTS OPERATED ABOVE 3 DAYS (NOT EARLY LAPAROSCOPIC CHOLECYSTECTOMY).

	No CV-DM comorbidity	CV-DM comorbidity	P-Value
Number of patients	183	150	-
Age (years)	47,9+14,5	66,9+13,3	0,3437
Male gender	74 (40,4%)	90 (60%)	**0,0004**
ASA score I/II and **III/IV**	176/7	81/69	**0,0001**
Positive clinical signs	88 (48%)	92 (61,3%)	**0,0202**
Positive imaging findings	148 (80,8%)	99 (66%)	**0,0025**
Complications (Clavien-Dindo I/II and **III/IV)**	3/3	14/6	0,6279
Mortality	0	0	1,0000

CV= cardiovascular; DM= diabetic

TABLE 7 - SUBGROUP OF PATIENTS OPERATED ABOVE 3 DAYS (NOT EARLY LAPAROSCOPIC CHOLECYSTECTOMY).

	No CV-DM comorbidity	CV-DM comorbidity	p-Value
Number of patients	183	150	-
Operative time (minutes)	79,1+36,6	98,3+46,3	0,7418
Conversion rate	11/183 (**6%**)	30/150 (**20%**)	**0,0002**
Post-operative Length of Stay (days)	3,2+5,2	4,8+6,9	0,8506

CV= cardiovascular; DM= diabetic

TABLE 8 - PATIENTS AFFECTED BY CARDIOVASCULAR-DIABETIC COMORBIDITY.

	EARLY LAPAROSCOPIC CHOLECYSTECTOMY (≦ 3 days)	NOT EARLY LAPAROSCOPIC CHOLECYSTECTOMY (>3 days)	p-Value
Conversion rate	8/31 (**25,8%**)	30/150 (**20%**)	0,4730

However, with wider experience and the improvement in pre- and postoperative care, laparoscopic surgery in patients taking anticoagulants is not contraindicated provided that the INR value is kept between 1.5 and 2.0 at the time of operation (28). The "early" (within 3 days) *versus* "not early" (after 3 days) or " very delayed" (after 6 weeks) laparoscopic approach in cases of acute cholecystitis has been debated over the last 20 years in international literature (38-45) and finally set by the 2013 Tokyo guidelines (2) in favor of an "early" procedure within 72 hours: but notwithstanding the timing of cholecystectomy in the daily management of patients presenting with acute cholecystitis is variable and controversial in clinical practice, even in spite of well-published guidelines from surgical societies such as SAGES and SSAT both advocating "early" cholecystectomy during same hospital admission (46). In clinical practice, medical wards admit patients affected by acute cholecystitis and initially treat them by antibiotic therapy: this conservative approach can be successful or not, and the time for referral to a surgical ward is depending upon this clinical situation. Two current approaches exist in the treatment of acute cholecystitis: (*1*) the traditional, conservative approach consisting of initial antibiotic therapy or percutaneous cholecystostomy followed by "not early" or "very delayed" cholecystectomy once inflammation has resolved; and (*2*) the preferred approach of "early" surgical intervention,

TABLE 9 - UNIVARIATE ANALYSIS OF 240 LAPAROSCOPIC CASES – PRE-OPERATIVE FACTORS AFFECTING CONVERSION RATE.

	Conversion	No Conversion	p-Value
Number of patients	17	223	-
Male sex	10 (59%)	95 (43%)	0,2134
BMI (kg/m2)	25,8±3,5	26,6±16,2	0,8394
ASA Class			0,0884
I-II	11 (65%)	187 (84%)	
III-IV	6 (35%)	36 (16%)	
Cardiovascular com.	13 (77%)	78 (35%)	**0,0012**
Diabetes	3 (18%)	17 (8%)	0,1578
Cardiovascular com. *and* Diabetes	2 (12%)	11 (5%)	0,2322
No Cardiovascular com. *and* No Diabetes	3 (18%)	139 (62%)	**0,0005**
Cardiovascular com. *or* Diabetes	14 (42%)	84 (38%)	**0,0001**
WBC positivity	8 (47%)	36 (16%)	**0,0046**
CRP positivity	8 (47%)	35 (16%)	**0.0039**
WBC (x10^9/L)	10,58±6,68	8,82±3,53	0,0682
Platelets (x10^9/L)	216,35±78,70	249,95±72,57	0,0686
INR	1,13±0,12	1,06±0,16	0,0789
Creatinine (microMol/L)	1,23±1,09	1,04±0,28	0,0541
Amilase (U/L)	62,63±30,37	69,53±51,01	0,9723
Lipase (U/L)	22,80±12,39	46,90±93,06	0,2879
Bilirubine (mg/dL)	1,18±1,22	0,97±0,76	0,2597
CRP (mg/dL)	13,66±14,24	5,57±9,86	**0,0009**
Positive clinical signs	10 (59%)	100 (45%)	0,3115
Positive imaging findings	8 (47%)	164 (74%)	0,1666

com. = comorbidity; CRP= C- reactive Protein; WBC= white blood cell count

TABLE 10 - MULTIVARIATE ANALYSIS OF 240 LAPAROSCOPIC CASES – PRE-OPERATIVE FACTORS AFFECTING CONVERSION RATE.

	p-Value	OR	CI95%
Cardiovascular com.	Ns	-	-
No Cardiovascular *and* no Diabetes	**0,002**	**7,722**	**2,156-27,664**
Cardiovascular *or* Diabetes	Ns	-	-
WBC positivity	Ns	-	-
CPR positivity	Ns	-	-

com. = comorbidity; CRP= C- reactive Protein; WBC= white blood cell count

ideally utilizing laparoscopic cholecystectomy within three days of admission. A laparoscopic cholecystectomy is suggested for grades I and even II of acute cholecystitis based on the Tokyo guidelines 2013, further recommending that cholecystectomy should be performed as soon as possible after admission-typically within 72 hours from the onset of symptoms (2). But in case of preoperative risk factors as diabetes or anticoagulant/antiplatelet therapy, the issue of timing is becoming particularly important in such group of patients, prone to development of acute gangrenous cholecystitis (diabetic subjects) and to intraoperative bleeding (cardiovascular patients). Our statistical analysis evaluated together di-

TABLE 11 - PATIENTS AFFECTED BY CARDIOVASCULAR-DIABETIC COMORBIDITY.

	EARLY LAPAROSCOPIC CHOLECYSTECTOMY (≦ 3 days)	NOT EARLY LAPAROSCOPIC CHOLECYSTECTOMY (>3 days)	VERY DELAYED LAPAROSCOPIC CHOLECYSTECTOMY (> 6 weeks)
Conversion rate	8/31 (**25,8%**)	30/150 (**20%**)	6/67 (**8,95%**)

abetes and cardiovascular comorbidity as pre-operative factors affecting conversion rate: in our series the "early" laparoscopic approach in diabetic/cardiovascular patients was not superior in terms of operative time, complications, length of stay and mortality to the control group, showing a significantly higher (p= 0.0147) conversion rate among diabetic/cardiovascular patients (25.8%) when compared to the control group (4.76%). Same results were obtained comparing diabetic/cardiovascular subjects to a control group among the "very delayed" subgroup of patients, confirming them as risk factors for a converted open procedure: the trend to conversion from laparoscopy to open cholecystectomy was higher (p= 0.0584) in the "early" subgroup (25.8%) *versus* the "very delayed" one (8.95%) among diabetic/cardiovascular subjects affected by acute cholecystitis, representing subsequently an high risk group for conversion especially when approached within 3 days. The monitoring group ("not early" group of patients operated after 3 days) confirmed the results, showing moreover among diabetic/cardiovascular patients a trend towards an higher conversion rate when comparing subjects operated within 3 days ("early"-25.8%), after 3 days ("not early"-20%) and after 6 weeks ("very delayed"-8.95%) (Table 11).

Conclusions

Our multi-center report from two different Institutions showed a significantly increased conversion rate from a laparoscopic approach to an open procedure for diabetic/cardiovascular patients affected by cholecystitis, especially within 3 days by the acute episode. Practical implications of our findings are represented by an increased acceptance by our surgical groups towards a "not early" or "very delayed" laparoscopic approach when patients are initially treated conservatively in medical wards: a prospective multi-center study will allow a more systematic collection of data, which would validate our retrospective findings providing more useful information for clinical practice.

Author contribution

All Authors gave substantial contributions to the conception, design, acquisition, analysis, and interpretation of data for the work.

All Authors drafted the work, revising it critically for important intellectual content.

All Authors gave their final approval of the version to be published.

All Authors agreed 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.

Conflict of interest/Financial support and sponsorship

None.

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