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A randomised clinical trial



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Does surgical experience really matter on the treatment approach to acute cholecystitis. A randomised clinical trial

AIM: Experienced surgeons usually prefer early laparoscopic cholecystectomy (ELC) instead of delayed laparoscopic cholecystectomy (DLC) for the treatment of acute cholecystitis (AC). However, the question remains, if ELC is also safe for beginner surgeons. This study compares ELC versus DLC for the treatment of AC as a beginner surgeon approach.

MATERIAL AND METHODS: In this prospective randomized clinical trial, patients suffering AC in their first 72 hours of pain were enrolled either in Group L (n:88); patients were treated surgically with ELC immediately or Group D (n:88); patients were first treated medically and then treated surgically with DLC 4-8 weeks later. All operations and medical treatments were done by the same beginner surgeon.

RESULTS: In Group L operation time was 60 (50-65) minutes, total hospital stay was 1.5 (1-7) days and total cost was 337.38±78.46 (287-827) USD. In Group D operation time was 50.5 (45-60) minutes, total hospital stay was 5.5(3-15) days and total cost was 499.29±199.38 (321-1506) USD. There were no significant differences regarding to the complications ($p>0.05$). Hospital stay and total costs were significantly higher in Group D ($p<0.001$).

CONCLUSIONS: This study indicates, that ELC can definitely be chosen as a treatment approach for AC even by beginner surgeons, considering that it reduces hospital stay and total cost.

KEY WORDS: Acute Cholecystitis, Delayed laparoscopic cholecystectomy, Early laparoscopic cholecystectomy, Surgical work experience

Introduction

Acute cholecystitis (AC) is the acute inflammation of the gallbladder primarily due to gall stones. This acute inflammation usually starts with the obstruction of the cystic duct. It is diagnosed with clinical symptoms, physical examination and radiological findings. Gallstones are a

significant health problem worldwide with a 10-15 % prevalence in developed countries and a 5.25 % prevalence in our country^{1,2}. Although not all gallstones are symptomatic, patients, who are suffering acute cholecystitis are one of the most common patient groups at the emergency services. Every year 23% of these asymptomatic gallstones become symptomatic, and acute cholecystitis has a similar incidence as acute appendicitis^{3,4}.

Although Laparoscopic cholecystectomy is the gold standard in cholecystectomy, there is no consensus regarding the timing of cholecystectomy. Formerly medical treatment of acute cholecystitis was common and surgical treatment was not done until 6-12 weeks after the acute period had ended⁵, which is why some older sur-

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ABBREVIATIONS

ELC: Early Laparoscopic Cholecystectomy

DLC: Delayed Laparoscopic Cholecystectomy

LC: Laparoscopic Cholecystectomy

CRP: c-reactive protein,

ALT: Alanine-amino-acid-transferase,

AST: Aspartate-amino-acid-transferase,
Transaminases: Alanine-amino-acid-transferase,
Aspartate-amino-acid-transferase)

GGT: Gamma-glutamyl transferase,

T.Bil: Total bilirubin,

D.Bil: Direct bilirubin

Endnotes: All costs were calculated in Turkish Liras (TRY) and according to Central Bank of Turkey exchange rates announced at 20.03.2017 were converted to United States of America Dollar (USD).
1 USD = 3.6381 TRY

geons believe that acute cholecystitis is a relative contraindication of laparoscopic cholecystectomy; however, some hospitals want to change their clinical approaches because of the developing outcomes of early laparoscopic cholecystectomy (ELC) ⁶.

Even though, lots of knowledge about the comparison of early laparoscopic cholecystectomy (ELC) versus delayed laparoscopic cholecystectomy (DLC) for the treatment of acute cholecystitis there has been only few knowledge considering the surgical work experience. Recent studies have proven that ELC in the first 72 hours after the symptoms of acute cholecystitis occur, has better benefits in terms of hospital stay and total costs compared to DLC without increase of complications by expert hepatobiliary surgeons ⁷.

This study examined the complications, mortality rates, cost-effectiveness and safety of ELC versus DLC among surgeons with less than 2 years of work experience.

Material and Methods

The study and the related procedures were conducted in compliance with guidelines approved by the Ethics Committee at Hamidiye Sisli Etfal Education and Research Hospital. Local ethics committee approved this study with a registration number of (2016/1141) and it is registered in Clinical Trials as NCT03122054. Written informed consent was obtained from all patients. The primary goal of the power analysis was to determine the total hospital stay costs, total hospital stay, operation time and complication rate. A post hoc analysis of the primary goal was performed, and the power was found to be 0,95 for n:176 (n₁:88; n₂:88). The study design was a prospective randomized clinical trial, which was

performed until reaching n=176. Patients suffering acute cholecystitis in the first 72 hours of pain were randomized into two groups by the on-shift nurse, who used the closed-envelope method. In Group L, early laparoscopic cholecystectomy was performed, whereas in Group D, delayed LC was performed 4-8 weeks after the acute attack. All operations and medical treatments were performed by surgeons with <2 years of surgical experience.

The patients' demographic features, laboratory results, radiological findings, operating time, hospital stay, complications, and conversion to open surgery were collected prospectively. Cost analysis was performed using our hospital's package program 'Panates HBYS' (Panates', Buca, Izmir, Turkey). The hospital costs included all costs, from hospital admission to discharge (e.g., the hospital overnight fee, patients' meals, drugs, operation, consultation and ICU costs).

DEFINITION OF ACUTE CHOLECISTITIS

Acute cholecystitis was diagnosed through a combination of clinical, radiological and laboratory findings. Clinically, right upper abdominal pain with right upper abdominal defense and rigidity were considered. Radiologically; abdominal ultrasonography was used for all patients and expanded gallbladder volume with wall thickness and stones inside were significant. From the laboratory results, leukocytosis or elevated C-reactive protein were observed and graded using the Tokyo Guideline 2013 diagnostic criteria and the severity grading of acute cholecystitis ⁸.

INCLUSION CRITERIAS

Inclusion criteria were as follows; patients with a diagnosis of acute cholecystitis, between age of 18 and 65 and clinical duration less than 72 hours.

EXCLUSION CRITERIAS

Exclusion criterias were as follows; a clinical duration longer than 72 hours, complicated acute cholecystitis (bilirubin >2gr/dl, elevated transaminases (>100 u/l) and cholestatic enzymes (gamma glutamyl transferase >50 u/l), ultrasonografically confirmed dilated intrahepatic or extrahepatic bile ducts, and elevated amylase levels three times more than normal range.

SURGICAL TECHNIQUE

All operations were performed by surgeons, who received laparoscopic surgery training during their residency

and having a surgical experience <2 years after residency. The operation team was composed of one general surgeon with surgical experience (as previously described), one resident surgeon in his 5th year of residency and one general surgical nurse.

All operations were performed with the patients under general anesthesia. First, a trocar was inserted with Hasson method (a subumbilical 1 cm vertical incision was made and the first 10-mm trocar (Versaport™ plus V2, Covidien, USA) was inserted under direct vision) and pneumoperitoneum was created with 12 mm Hg pressure. The second 10-mm trocar was inserted from subxiphoidal area. Two 5-mm trocars were inserted in the right upper quadrant area. After general intrabdominal exploration, dissection was started to ensure safe-view of Calot triangle. In case of quite tough gallbladder for gripping, gallbladder was drained with a gray intravenous cannula. Cystic artery and cystic duct were separately dissected and twice ligated with Endo Clip™ II ML (Covidien, USA). The gallbladder was carefully dissected from the liver bed and removed from the abdomen through the subumbilical incision. Saline lavage was performed if the operation area was not clear or contaminated with bile. In case of suspicious Calot's triangle

anatomy or the need for hard dissection, an experienced hepatobiliary surgeon was invited to participate in the operation.

STATISTICAL ANALYSIS

Statistical analysis was done with SPSS 15 (SPSS Inc, Chicago, Illinois). Descriptive statistics were presented as mean±standard deviation, frequency, percentage, minimum and maximum. Chi-square test was used for categorical variables. Mann-Whitney U test was used if the groups were not in normal distribution. P value <0.05 was considered statistically significant.

Results

In total 176 patients were eligible for this study. Patients in Group L (n=88) underwent ELC and those in Group D (n=88) underwent DLC. Both groups had similar demographical data and co-morbidities, which were shown in Table I. Both groups have similar laboratory findings that were shown in Table II. Both groups have

TABLE I - Comparative Analysis of Demographics.

		Group L n:88	Group Dn:88	p value
Median Age, years	Median (IQR)	48,5 (41-55)	54 (40-60)	NS
Gender n (%)	Male	22 (25.0)	27 (30.7)	NS
	Female	66 (75.0)	61 (69.3)	NS
Co-morbidities n (%)	HT	15 (17.0)	18 (20.5)	NS
	DM	12 (13.6)	11 (12.5)	NS
	CAD	2 (2.3)	3 (3.4)	NS
	COPD	2 (2.3)	1 (1.1)	NS
		64 (72.7)	65 (73.9)	NS
ASA Score I n (%)		15 (17)	13 (14.7)	NS
ASA Score II n (%)		9 (10.3)	10 (11.4)	NS
ASA Score III n (%)		35 (43.8)	34 (38.6)	NS
Severity Grade of acute cholecystitis n (%)	Grade I	45 (51.1)	47 (53.4)	NS
	Grade II	8 (9.1)	7 (8)	NS
	Grade III			

IQR: Interquartile range, COPD: Chronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease, DM: Diabetes Mellitus, HT: Hypertension, p<0.05 is considered statistically significant different, p>0.05 is considered as statistically not significant different (NS).

TABLE II - Initial Laboratory findings.

	Group L n:88	Group Dn:88	p value
WBC 10 ³ /uL	12.38±3.48	12.68±4.51	NS
CRP mg/L	54±45	48±39	NS
ALT U/L	71±25	65±31	NS
AST U/L	63±31	59±40	NS
GGT U/L	49±14	45±9	NS
Amylase U/L	80±42	74±39	NS
T.B mg/dL	0.67±0.31	0.65±0.28	NS

WBC: White blood cell, CRP: C-reactive protein, ALT: Alanine-amino-acid-transferase, AST: Aspartate-amino-acid-transferase, GGT: Gamma-glutamyl transferase, T.B: Total bilirubin, p<0.05 is considered statistically significant.

similar severity grade of acute cholecystitis that were shown in Table I.

All operations were started using laparoscopic approach. In Group L, all operations were able to be finished laparoscopically. In group D, only two operations were converted to open surgery. Before conversion to open surgery, an experienced hepatobiliary surgeon was called to assess the operating field and asked to help for decision of conversion to open surgery. Both conversions were due to inability to ensure view of safety. There has been no statistically significant difference between the groups considering conversion to open surgery ($p>0.05$). Mirizzi Syndrome type III was detected in one patient in Group D. Median operating time was 50.5 (45-60) minutes in Group D (Table III). Three patients in both groups were observed in intensive care unit (ICU) postoperatively. There was no statistically significant difference considering intensive care unit stay in both Groups. [1 in Group L and 1.3 ± 0.58 days in Group D ($p>0.05$)]. Other complications included surgical side infection (2 in Group L and 2 in Group D) and postoperative ileus (1 in Group L and 0 in Group D). All complications were shown in Table III and there was no statistically significant difference between the groups.

In Group L, total hospital stay was 1.5 (1-7) days and total cost was 337.38 ± 78.46 (287-827) USD and the

operation time was 60 (50-65) minutes. In Group D, total hospital stay was 5.5 (3-15) days. Cost for initial hospital stay was 150.87 ± 113.4 USD whereas second hospital stay cost was 348.42 ± 122.61 USD (with a total cost of 499.29 ± 199.38 USD). Delayed period between the first attack and the operation was 7.12 ± 0.98 weeks. The duration of hospital stay and total hospital cost were significantly higher in Group D ($p<0.05$). (Table IV) There were no deaths in either group.

Discussion

This prospective study showed similar results concerning the surgical safety of ELC compared to DLC. ELC might be a good choice when the total length of hospital stay and total costs are evaluated. This study also provides objective results because all operations and medical treatments were performed by surgeons with <2 years of surgical experience.

ELC demonstrated significant benefits in acute cholecystitis management compared to DLC, even when performed by junior surgeons in this study. The first outcome in this study was that there were no statistically significant between-group differences regarding postoperative complications and conversion to open surgery. Recent

TABLE III - Outcome and Complications

	Group L n:88	Group Dn:88	p value
Total Length of hospital stay (Days) Median (IQR)	1,5 (1-7)	5,5 (3-15)	<0.001
Operation time (Minutes) Median (IQR)	60 (50-65)	50,5 (45-60)	<0.001
Conversion rates n(%)	0 (0.0)	2 (2.3 %)	NS
Frequency of calling a senior HPB surgeon n(%)	0	2 (2.3)	NS
Clavian Dindo Classification			
Grade I n(%)	2 (2.3)	2 (2.3)	NS
Grade II n(%)	1 (1.1)		NS
Grade III a n(%)		1 (1.1)	NS
ICU stay n(%)	3 (3.4)	3 (3.4)	NS
ICU stay (days)	1.0 ± 0.0	1.33 ± 0.58	0.956
Complication	3 (3.4)	3 (3.4)	1.000
CBD Injury	0 (0.0)	1 (1.1)	0.946
Postop Ileus	1 (1.1)	0 (0.0)	0.946
Wound side infection	2 (2.3)	2 (2.3)	1.000

ICU: intensive care unit, IQR: Interquartile range $p<0.05$ is considered statistically significant different, $p>0.05$ is considered as statistically not significant different (NS).

TABLE IV - Costs*

	Grup L Mean \pm SD/min-max	Grup D Mean \pm SD/min-max	P value
1st Hospital stay cost	$337.38\pm78.46/287-827$	$150.87\pm113.4/34-724$	
2nd Hospital stay cost		$348.42\pm122.61/287-1090$	
Total Hospital stay cost	$337.38\pm78.46/287-827$	$499.29\pm199.38/321-1506$	<0.001

*cost were calculated in Turkish Lira and according to Central Bank of Turkey exchange rates announced at 20.03.2017 were converted to United States of America Dollar (USD). 1 USD = 3.6381 TRY SD: standard deviation $p<0.05$ is considered statistically significant.

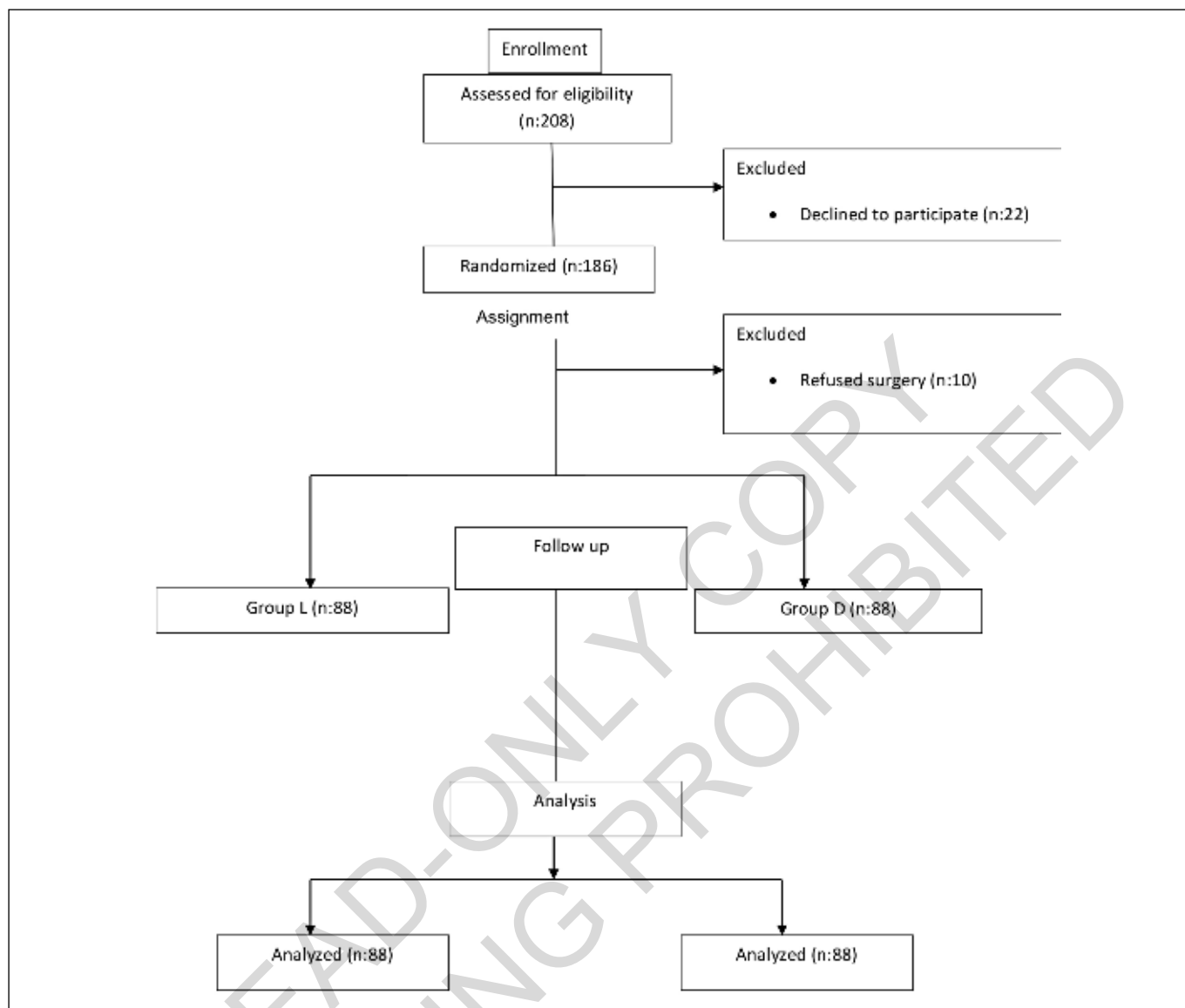


Fig. 1: Consort Flow Diagram.

studies have shown that early conversion does not seem to affect the mortality and length of hospital stay⁹. The second outcome in this study was that, although the operating time was statistically higher in the ELC group, the total hospital stay and total costs were statistically lower in this group compared to the DLC group. The final outcome in this study was that the treatment choice did not cause mortality in either group.

Just as the same in other laparoscopic surgery techniques, laparoscopic cholecystectomy (LC) also relies on visual perception, without feeling the tissue and sense of depth. Despite all perfections in technology, surgeons are still unable to feel the tissue and depth in laparoscopy. A decade ago, studies showed us that duct misidentification and subsequent erroneous transection or clipping were the most common causes of bile duct injury during laparoscopy⁸. In most cases surgeons failed to recognize

a problem during the operation, even though seeing that there was an abnormality at the surgical field⁹. This situation is a phenomenon called cognitive fixation¹¹. More over 97 % of the bile duct injuries were caused because of that phenomenon, not related to surgical skill, knowledge, or judgment¹¹. For safe surgery the most important thing to consider is to follow the guidelines of 'critical view of safety'¹². We also observed an abnormal situation during the surgery of one patient in Group D, in which the operation was converted to open surgery because Mirizzi Syndrome type III was detected.

Recent studies have shown that bile duct injury following LC has a rate of 0.08 %, which is similar to older data of complication rates in open cholecystectomy¹³. However, some other studies indicate that LC has still a higher bile duct injury rate than open cholecystectomy has¹⁴. However, the surgical approach for acute cho-

lecystitis is still debatable. Some studies reported that ELC for acute cholecystitis has high conversion to open surgery rates ranging 6% to 35%^{15,16}. These rates and additionally high bile duct injury rates were reasons for controversy in ELC. However, recent studies had opposite findings as ELC done by experienced surgeons within 72 hours of onset of acute cholecystitis symptoms had better outcomes in both morbidity and hospital stay costs^{17,18}. There has been few information on which LC will be easy or which LC will be difficult. Studies on this issue are available in the literature. One of these studies was Diaz-Flores et al. In this study, patients with CRP levels above 11 mg/dL were predicted to have difficult LC¹⁹. Recent studies have shown that these factors significantly associated with conversion were: age over 60 years, diabetes, previous supramesocolic abdominal surgery, ultrasound signs of cholecystitis, white cell count over $9 \times 10^3/\text{dl}$, previous acute myocardial infarction and preoperative ERCP, intraoperative²⁰ For preoperative ERCP, we need to say that some studies shown us preoperative ERCP have no effect on the rate of conversion to open surgery²¹.

It is very well known that laparoscopic surgery has several advantages and currently is the gold standard for several abdominal procedures, including cholecystectomy^{22,23}. ELC is superior compared to DLC in terms of safety, short hospital stay and low costs with comparable morbidity and mortality²⁴. In the light of these findings, unfortunately ELC for acute cholecystitis is still recommended to be done by experienced laparoscopic surgeons²⁵. In this present study, junior surgeons that have been trained LC during residency, performed both ELC and DLC. Surgeons, who completed their residency in the early 2000s were dependent on animal laboratories and post-graduate courses to learn laparoscopy. Nowadays, all surgeons have laparoscopic training during their residency period and this tendency ensures lower complication rates, particularly bile duct injuries¹⁰. Therefore, we believe that no matter the grade of the surgeon is, ELC should be the first choice of treatment in acute cholecystitis, when laparoscopic training was received during residency.

This study examined a study group with the following inclusion criteria: diagnosis of acute cholecystitis, patient age between 18 and 65 years of age, and a clinical duration of less than 72 hours. Another limitation of this study is that there is no information about the pathological reports.

Conclusion

We concluded that in the current laparoscopic era, early surgical treatment of acute cholecystectomy could be safely managed with laparoscopic cholecystectomy even by junior surgeons (surgical experience <2 years after residency) who were trained for laparoscopic surgery

during their residency. This approach reduces hospital stay and costs, which is why surgical work experience should not affect the treatment choice, and ELC should be preferred for acute cholecystitis treatment.

Riassunto

I chirurghi esperti di solito preferiscono eseguire la colecistectomia laparoscopica precocemente (ELC) e non la colecistectomia laparoscopica ritardata (DLC) per il trattamento della colecistite acuta (AC). Tuttavia, rimane la domanda, se l'ELC è sicura anche per i chirurghi principianti. Questo studio si è proposto di dare risposta a questa domanda; ELC o non la DLC per il trattamento della CA come approccio chirurgico per principianti. Si è proceduto con uno studio clinico prospettico e randomizzato: gli 88 pazienti sofferenti di AC da non più di 72 ore di dolore sono stati arruolati nel gruppo L e trattati chirurgicamente con ELC immediata; gli 88 pazienti del gruppo D sono stati inizialmente trattati con terapia medica e successivamente colecistectomizzati con DLC 4-8 settimane dopo. Tutte le operazioni e i trattamenti medici sono stati eseguiti dallo stesso chirurgo principiante.

nei pazienti del gruppo L è stato di 60 minuti in media (50-65), con degenza totale in ospedale è stata di 1,5 giorni di media (1-7) giorni e il costo totale è stato di $337,38 \pm 78,46$ (287-827) USD. Nel gruppo D il tempo di intervento è stato di 50,5 minuti in media (45-60), la degenza totale in ospedale è stata in media di 5,5 giorni (da 3 a 15), e il costo totale è stato di $499,29 \pm 199,38$ (321-1506) USD. Non ci sono state differenze significative per quanto riguarda le complicanze ($p > 0,05$). La degenza ospedaliera e i costi totali sono risultati significativamente più elevati nel gruppo D ($p < 0,001$).

In conclusione questo studio indica che l'ELC può sicuramente essere scelta come approccio terapeutico per la CA anche dai chirurghi principianti, considerando che riduce la degenza ospedaliera e il costo totale.

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