Original Article

# End-stage renal disease is a risk factor for complex laparoscopic cholecystectomy in patients waiting for renal transplantation

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## Abstract

**Introduction:** To date, there are no studies investigating whether laparoscopic cholecystectomy (LC) is technically more complex in patients waiting for kidney transplant. The aim of this study is to create a user-friendly score to identify high-risk cases for complex LC integrating end-stage renal disease (ESRD).

**Materials and Methods:** We retrospectively analysed 321 patients undergoing LC during the period 2014–2016. Two groups were compared: ESRD group ($n = 25$) versus control group ($n = 296$). Concerning statistical analysis, continuous variables were compared using Kruskal–Wallis' test, dummy variables with Chi-square test or Fisher's exact test when appropriate. A multivariable logistic regression analysis was performed to identify risk factors for complex LC. A backward conditional method was used to design the final model.

**Results:** Seventy out of 321 (21.8%) cases were considered as complex, with a higher prevalence in the ESRD group (32.0 vs. 20.9%; $P = 0.2$). Using a multivariable logistic regression analysis, we formulated a score based on the independent risk factors for complex LC: 4×(previous cholecystitis) +5 × (previous ESRD) +1 × (age per decade) +2 × (previous open abdominal surgery). High-risk cases (score ≥ 10) were more commonly reported in the ESRD group (72.0 vs. 24.7%; $P < 0.0001$).

**Conclusion:** Although several scores investigating the risk for complex LC have been proposed, none of them has focused on ESRD. This is the first series demonstrating that ESRD is an independent risk factor for technical complexity in LC. We developed a score to offer surgeons an extra tool for pre-operative evaluation of patients requiring LC.

**Keywords:** Cholecystectomy, dialysis, gallbladder, kidney transplantation

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## INTRODUCTION

Gallbladder diseases are among everyday surgical indications. Nowadays, laparoscopic cholecystectomy (LC) is the gold standard treatment for symptomatic gallstones, also in transplanted patients.[1]

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Gallbladder rupture during LC ranges from 3.5% in normal conditions up to 25% in the case of acute cholecystitis or previous upper abdominal surgery.[2] The reported incidence of bleeding in general population varies from 0.03% to 10%.[3] There is poor evidence of increased technical complexity in patients with end-stage renal disease (ESRD). We routinely perform LC in patients waiting for kidney transplantation (KT). We set up a retrospective case–control study to investigate the possible role of ESRD as a cause of difficult LC.

## SUBJECTS AND METHODS

Three hundred and twenty-one patients were admitted to our surgical department due to cholelithiasis between January 2014 and December 2016. Twenty-five patients were affected by ESRD requiring renal replacement therapy (RRT), while 296 had a normal renal function.

The presence of comorbidities, body mass index (BMI), drug history, previous abdominal surgery, history of previous endoscopic retrograde cholangiopancreatography (ERCP), cholecystitis and/or pancreatitis were evaluated in each case.

LC was defined complex in the case of gallbladder wall rupture during handling and/or a bleeding from the gallbladder fossa.

From a technical point of view, LC was always performed using the standard four-port method with 30° laparoscope in all cases. After induction of pneumoperitoneum, we retracted the gallbladder infundibulum to expose the Calot's triangle. Once the area of the hilum of the gallbladder was reached, cystic duct and artery were dissected, clipped and divided. Then, the gallbladder was progressively removed from the infundibulum towards the fundus. All the procedures were performed by the same experienced surgeon (CG).

### Statistical analysis

Continuous variables were reported as medians and interquartile ranges (IQR). Dummy variables were reported as numbers and percentages. Continuous variables were compared using the Kruskal–Wallis test; dummy variables were compared using the Chi-square test or the Fisher's exact test when appropriate.

A multivariable logistic regression analysis was performed for the evaluation of the risk factors for complex LC. A backward conditional method was used to design the final model. Beta-coefficients, standard errors, odds ratios (OR) and 95% confidence intervals (CI) (95% CI) were reported. Variables with a $P < 0.05$ were considered statistically significant. SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA) was used.

## RESULTS

We stratified the entire population according to the necessity of RRT at the moment of LC, and we identified two groups: the ESRD group ($n = 25$) and the control group ($n = 296$).

The ESRD group ($n = 25$) was composed of 16 men and nine women (64.0 vs. 36.0%) with a median age of 52 years (IQR: 45–58). In five out of 25 (20.0%) cases, autosomal dominant polycystic kidney disease was the cause of ESRD. The control group ($n = 296$) was composed of 161 men and 135 women (54.4 vs. 45.6%), with a median age of 56 years (IQR: 45–61).

With regard to intra-operative complications, a total of 70 out of 321 (21.8%) cases were characterised by complicated gallbladder removal, with 46 (14.3%) cases ending in its rupture during the dissection and 24 (7.5%) cases of gallbladder fossa bleeding: in all cases, complications were managed laparoscopically with no need for conversion to open surgery [Table 1].

Comparing the two groups, no significant differences were observed in terms of median patient age (52 vs. 56 years; $P = 0.3$), male gender (64.0 vs. 54.4%; $P = 0.2$) and underlying comorbidities, though the ESRD group showed a trend towards a higher prevalence of type 2 diabetes mellitus (16.0 vs. 9.5; $P = 0.2$) and arterial hypertension (24.0 vs. 15.5%; $P = 0.2$). Similar percentages of patients with high BMI (≥30), use of tobacco and anticoagulants were observed between the two groups.

As expected, in the control group, patients often underwent LC for a gallstones-related complication: previous cholecystitis was reported in 30.7% versus 8.0% of cases ($P = 0.009$). Although these data were not statistically significant, also previous pancreatitis episodes (12.5 vs. 4.0%; $P = 0.2$) and previous ERCP (11.8 vs. 4.0%; $P = 0.2$) were more common in the control group. A higher percentage of previous abdominal surgery was reported in the control group as well (29.1 vs. 8.0; $P = 0.02$).

Even if these differences might predict a greater difficulty of LC in the control group, no statistically significant differences were observed between the two groups. Conversely, the ESRD group displayed a trend towards a higher incidence of adverse events, in terms of bleeding (12.0 vs. 7.1%; $P = 0.3$), rupture

**Table 1: Comparison between the end-stage renal disease and comparison-group in terms of demographics, history of gallbladder-related diseases and complexity of laparoscopic cholecystectomy**

| Variables | ESRD group (*n*=25) | Control group (*n*=296) | *P* |
|---|---|---|---|
| | Median (IQR) or, *n* (%) | | |
| Age (years) | 52 (45-58) | 56 (45-61) | 0.3 |
| Male gender | 16 (64.0) | 161 (54.4) | 0.2 |
| History of DM2 | 4 (16.0) | 28 (9.5) | 0.2 |
| History of HPT | 6 (24.0) | 46 (15.5) | 0.2 |
| BMI ≥30 | 3 (12.0) | 46 (15.5) | 0.5 |
| Smoking | 4 (16.0) | 36 (12.2) | 0.4 |
| Use of anticoagulants | 5 (20.0) | 65 (22.0) | 0.5 |
| Previous open abdominal surgery | 2 (8.0) | 86 (29.1) | 0.02 |
| Previous pancreatitis | 1 (4.0) | 37 (12.5) | 0.2 |
| Previous cholecystitis | 2 (8.0) | 91 (30.7) | 0.009 |
| Previous ERCP | 1 (4.0) | 35 (11.8) | 0.2 |
| Surgical complication during LC | | | |
| Bleeding | 3 (12.0) | 21 (7.1) | 0.3 |
| Rupture | 5 (20.0) | 41 (13.9) | 0.3 |
| Combined complication | 8 (32.0) | 62 (20.9) | 0.2 |

DM2: Type 2 diabetes mellitus, BMI: Body mass index, ERCP: Endoscopic Retrograde Cholangio-Pancreatography, LC: Laparoscopic cholecystectomy, ESRD: End-stage renal disease, IQR: Interquartile ranges, HPT: Arterial hypertension

(20.0 vs. 13.9%; $P = 0.3$) and consequently, overall complications (32.0 vs. 20.9%; $P = 0.2$) [Table 1].

We run a multivariable logistic regression analysis to identify the independent risk factors for complex LC. History of ESRD was an independent risk factor for higher complexity during LC (OR = 4.9; 95% CI = 1.8–13.5; *P* value = 0.002). Other consistent risk factors were history of cholecystitis (OR = 3.8; 95% CI = 2.0–7.4; *P* value < 0.0001), patient age-per decade (OR = 1.4; 95% CI = 1.1–1.7; $P = 0.007$) and previous upper abdominal surgery (OR = 2.2; 95% CI = 1.2–4.3; $P = 0.02$) [Table 2].

Based on the OR of the multivariate analysis, we developed a user-friendly score able to predict a complex LC, according to the following equation:

4 × (previous cholecystitis) +5 × (previous ESRD) +1 × (age per decade) +2 × (previous open abdominal surgery)

In accordance with this equation, a higher median score value was observed in the ESRD group (10 vs. 7; $P < 0.0001$). The entire population was then divided into three groups according to the score points: (1) score 0–4 ($n = 97$), (2) score 5–9 ($n = 133$) and (3) score ≥10 ($n = 91$). The distribution of these three groups was uneven between patients with or without ESRD, with a greater prevalence of patients with score ≥10 in the ESRD group (72.0 vs. 24.7%; $P < 0.0001$).

With respect to the incidence of complex LC according to the score, only 3.1% of cases were reported in patients with a score 0–4. The intermediate group (score 5–9) had 21.8% of complex LC. Patients showing a score ≥10 had the highest percentage of complex cases (41.8%) [Figure 1].

As shown in Table 3, all the possible combinations of the score are reported, showing the age thresholds to consider in relation to the simultaneous presence of the other risk factors.

## DISCUSSION

Gallstones are commonly detected during ultrasound scan in ESRD patients waiting for KT.[4] There is no clear indication on the need to perform a prophylactic LC in these patients. However, LC in transplanted patients can be a high-risk procedure since cholecystitis, cholangitis, or pancreatitis after KT can represent dangerous complications. There is some evidence that transplanted patients are more prone to experience these complications when compared to normal population, mainly due to their immunodepression.[5] An additive relationship has been described between the severity of biliary complications and intensity of immunosuppression.[6] Moreover, LC is more challenging in case of complicated cholecystitis.[7] On these grounds, several authors advocate prophylactic cholecystectomy in asymptomatic patients before transplantation to elude serious morbidity and increased mortality, when diagnosis of gallstones is established.[4,6,8]

In our case series, we reported a higher rate of difficult LC in ESRD patients. Thus, we investigated ESRD as a possible risk factor able to predict surgical difficulties.

A number of pre-operative scoring systems for LC are described in literature, reporting signs (e.g. the presence of palpable gallbladder) and pre-operative imaging findings.[9] Previous cholecystitis and ERCP are well-recognised risk factors increasing the complexity of the procedure.[10] Surgical difficulty reflects three contributing factors: patient's

**Table 2: Multivariable logistic regression analysis for the risk of complex laparoscopic cholecystectomy**

| Variables | ß | SE | OR | 95% CI | | *P* |
|---|---|---|---|---|---|---|
| | | | | Lower | Upper | |
| Previous episode(s) of cholecystitis | 1.3 | 0.3 | 3.8 | 2.0 | 7.4 | <0.0001 |
| History of ESRD | 1.6 | 0.5 | 4.9 | 1.8 | 13.5 | 0.002 |
| Patient age (×10 years) | 0.3 | 0.1 | 1.4 | 1.1 | 1.7 | 0.007 |
| Previous open abdominal surgery | 0.8 | 0.3 | 2.2 | 1.2 | 4.3 | 0.02 |
| Constant | −3.9 | 0.6 | 0.02 | - | - | <0.0001 |

Hosmer-Lemeshow test=6.2; *P*=0.6. The following variables were initially included in the multivariable analysis and then elided during the step-by-step backward conditional method: Male gender, history of DM2, history of HPT, BMI >30, smoking, use of anticoagulants, previous pancreatitis, ADPKD. SE: Standard error, OR: Odds ratio, CI: Confidence intervals, ESRD: End-stage renal disease, DM2: Type 2 diabetes mellitus, HPT: Arterial hypertension, BMI: Body mass index, ADPKD: Autosomal dominant polycystic kidney disease

**Table 3: Different combinations of patients according to the score points**

| |
|---|
| Very low risk of complex LC: Score 0-4 |
| Age 18-49 years, no other risk factor |
| Age 18-29 years, previous open abdominal surgery |
| Intermediate risk of complex LC: Score 5-9 |
| Age ≥50 years, no other risk factor |
| Age 18-59 years, previous cholecystitis |
| Age 18-49 years, ESRD |
| Age 18-79 years, previous open abdominal surgery |
| High risk of complex LC: Score ≥10 |
| Any age, previous cholecystitis + ESRD + previous open abdominal surgery |
| Any age, previous cholecystitis + ESRD |
| Age ≥60 years, previous cholecystitis |
| Age ≥50 years, ESRD |
| Age ≥80 years, previous open abdominal surgery |
| Age ≥40 years, previous cholecystitis + previous open abdominal surgery |
| Age ≥30 years, ESRD + previous open abdominal surgery |

LC: Laparoscopic cholecystectomy, ESRD: End-stage renal disease

features, nature of the disease and surgeon's skills. Under this scheme, Planells Roig *et al.* proposed the Surgical Complexity Classification Index divided in three chapters: the first considering technical complexity, obesity and gender, the second categorising age and the third listing comorbidities. The authors reasonably support the hypothesis that pre-operative characteristics influence the duration of surgery and as a result, surgical complications, hospital stay and costs.[11] Accordingly, most scores focus on pre-operative parameters, since they are committed to set benchmarks for administrative purposes.[9,11] A few investigate the degree of surgical complexity.[9,11,12] Sugrue *et al.* put forward their own score featuring intraoperative findings. It is centred on five key aspects: (1) gallbladder appearance and amount of adhesions, (2) degree of distension/contracture of the gallbladder, (3) ease of access, (4) local/septic complications and (5) time taken to identify the cystic artery and duct. Even this scoring system has some limitations: it is not validated in a large series, there is great subjectivity in estimating the

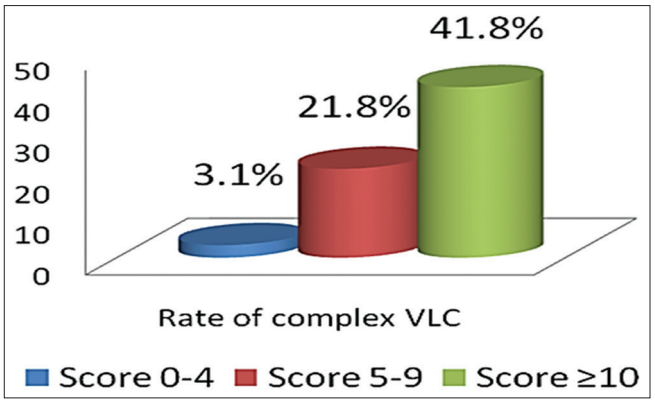


**Figure 1:** Rates of complex VLC in the three groups according to the score

amount of adhesions and it is not possible to predict tenacity of adhesions preoperatively.[9]

Vivek *et al.* developed a score ranging from 0 to 44, with the threshold to predict difficult LC set at nine. They comprehensively included pre-operative, ultrasonographic and intra-operative findings. Seven endpoints of surgical complexity were enumerated: umbilical port access, gallbladder grasping, adhesiolysis, Calot's triangle dissection, duct and artery clipping, gallbladder extraction. It is remarkable that the score yielded an area under receiver operator curve of 0.956.[12]

Among predictors, the authors added to anatomy liver-specific conditions like cirrhosis. As a matter of fact, cholelithiasis is more common in cirrhotic patients than in general population, and its approach is particularly cumbersome in this scenery.[13]

In our experienced, we noticed that, often, there is no clear plane between gallbladder and its fossa in patients in RRT and this constitutes a major risk for intra-operative bleeding and gallbladder's rupture during handling.[14] Unfortunately, we neither documented the presence of cirrhosis and derangement of hepato-pancreatic enzymes' profiles nor reported data on stones characteristics or anatomical features, parameters heralding difficult LC. Nevertheless, we emphasised and demonstrated a role for ESRD in influencing technical complexity of LC.

Terminal nephropathy is collaterally but not specifically encompassed in a number of surgical risk classification systems, such as APACHE II, POSSUM, MPI and ASA. Yet, they are all general and non-specific since they ignore intrinsic nature of the procedures.[11]

Due to the lack of data from literature, we can speculate on pathogenesis for our findings. The absence of cleavage

between gallbladder and liver is likely to originate from inflammation. Systemic inflammation notoriously coexists nephropathy and it is a main target in renal replacement strategies.[15] Furthermore, when used, peritoneal dialysis causes thickening of peritoneum and renal cysts might occasionally induce local peritoneal reaction through bleeding and infection.

Our study is limited in that our small series is retrospective and our score lacks external validation. Further investigation on markers of systemic inflammatory response and on histology is required, to confirm or disprove our assumptions on aetiology.

## CONCLUSION

ESRD is a risk factor for complexity in LC. A user-friendly score has been developed with the intent to pre-operatively help the surgeon in the management of patients waiting for kidney transplant requiring LC. Further external validation of this score is warranted.

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### Conflicts of interest
There are no conflicts of interest.

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