DOI: 10.4274/forbes.galenos.2026.87609
Forbes J Med 2026;7:15-22

Original Article

Biochemical and Hematological Markers for Predicting Difficult Laparoscopic Cholecystectomy in Patients Aged ≥65 Years: A Retrospective Cohort Study

Ozan Barış NAMDAROĞLU[1], Ferhat DEMİRCİ[2], Fatma DİKİŞER[1], Beyza GÜMÜŞTEKİN[1]

[1]University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Clinic of General Surgery, İzmir, Türkiye
[2]University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Clinic of Medical Biochemistry, İzmir, Türkiye

Cite as: Namdaroğlu OB, Demirci F, Dikişer F, Gümüştekin B. Biochemical and hematological markers for predicting difficult laparoscopic cholecystectomy in patients aged ≥65 years: a retrospective cohort study. Forbes J Med. 2026;7:15-22

ABSTRACT

Objective: To identify factors associated with difficult laparoscopic cholecystectomy (DLC) in patients aged 65 years and older and to evaluate the predictive value of inflammatory markers.

Methods: This single-center retrospective cohort study included patients aged 65 years and older who underwent laparoscopic cholecystectomy between 2015 and 2025. Difficult surgery was defined as conversion to open surgery and/or subtotal (bail-out) cholecystectomy and/or operative time of 120 minutes or longer. The C-reactive protein-to-albumin (CAR) ratio was calculated as C-reactive protein (CRP) divided by albumin. Multivariable logistic regression was used to identify independent predictors.

Results: A total of 726 patients were analyzed; the median age was 70 years (25^{th}–75^{th} percentile, 67–74), and 35.7% were male. Surgical difficulty occurred in 276 patients (38.0%). Conversion to open surgery occurred in 95 patients (13.1%) and was most commonly due to unsafe or uncertain anatomy (89.5% of conversions). The difficult group had a longer hospital stay (median 4 days compared with 1 day), a greater need for intensive care (34.8% compared with 8.4%), and a higher 30-day mortality (2.9% compared with 0.4%). Independent predictors were: acute cholecystitis [adjusted odds ratio (aOR) 8.79; 95% confidence interval (CI): 2.00–38.73]; a higher log-transformed CAR ratio (aOR): 1.45; 95% CI: 1.29–1.63); and male sex aOR: 1.44; 95% CI: 1.02–2.03).

Conclusion: In older adults, DLC are common and associated with worse perioperative outcomes. The CAR ratio may support preoperative risk stratification and operative planning in this population.

Keywords: Cholecystectomy, aged, C-reactive protein, albumin

Received: 16.02.2026
Accepted: 04.03.2026
Epub: 06.03.2026
Publication Date: 13.03.2026

Corresponding Author:
Ozan Barış NAMDAROĞLU
University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Department of General Surgery, İzmir, Türkiye
ozannamdaroglu@yahoo.com
ORCID ID: 0000-0001-5195-307X

INTRODUCTION

Laparoscopic cholecystectomy is the standard surgical approach for symptomatic gallstone disease. In older patients, a higher burden of comorbidities and a potentially more severe inflammatory course may increase technical difficulty, including adhesions, edema, and obscured anatomy. These factors can prolong operative time and increase the need for bail-out procedures or conversion to open surgery.[1-3]

The consequences of a difficult cholecystectomy extend beyond technical complexity and may translate into clinically meaningful outcomes, such as increased intraoperative complications, postoperative morbidity, intensive care unit (ICU) requirements, and longer hospital stays.[1,2] Therefore, objective preoperative risk estimation—particularly in patients aged ≥65 years—is important for operating room planning, anticipating bail-out strategies, and improving preoperative counseling.

Several clinical scoring systems and imaging-based predictors have been proposed to identify difficult cholecystectomies. However, in real-world retrospective datasets, these variables are not always recorded in a standardized or sufficiently granular manner, limiting

their consistent use, especially in large cohorts. For this reason, we adopted an approach based on objective and reproducible laboratory parameters routinely obtained at initial presentation.

C-reactive protein (CRP) reflects the acute-phase response, whereas albumin is inversely related to inflammation and serves as a marker of overall physiological reserve. The CRP/to-albumin ratio (CAR), calculated as CRP (mg/L) divided by albumin (g/dL), combines both parameters into a single measure and has been evaluated as a predictor of difficult laparoscopic cholecystectomy (DLC) in patients with acute cholecystitis.[4] The neutrophil-to-lymphocyte ratio (NLR) is another practical marker of systemic inflammatory response and has been associated with cholecystitis severity.[5] The aim of this study was to identify clinical features associated with difficult surgery during laparoscopic cholecystectomy in patients aged ≥65 years and to assess the predictive performance of readily available laboratory markers such as CAR and NLR.

METHODS

Study Design and Patient Selection

This was a single-center, retrospective, observational cohort study. Consecutive patients aged ≥65 years who underwent laparoscopic cholecystectomy at University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital between January 2015 and June 2025 were evaluated. Data were extracted from electronic medical records and operative/anesthesia notes.

Inclusion criteria were age ≥65 years and patients in whom laparoscopic cholecystectomy was initiated as the primary surgical procedure during the study period, regardless of intraoperative conversion to open surgery or subtotal (bail-out) cholecystectomy.

Exclusion criteria included primary open cholecystectomy (n=16), laparoscopic cholecystectomy performed concomitantly with another major abdominal procedure, missing CRP or albumin values at admission (n=8), and incomplete operative records (n=3) (Figure 1).

Demographic characteristics (age, sex), urgency (elective vs. emergency), comorbidities, American Society of Anesthesiologists (ASA) class, anticoagulant use, laboratory parameters (complete blood count and biochemistry), and perioperative clinical/surgical variables were recorded. Laboratory values were obtained from blood samples collected at the time of initial presentation. Anticoagulant use included vitamin K antagonists (warfarin), direct oral anticoagulants (apixaban, rivaroxaban, dabigatran), and antiplatelet agents (acetylsalicylic acid and P2Y12 inhibitors such as clopidogrel), all managed according to institutional perioperative protocols. CAR was calculated as CRP (mg/L)/albumin(g/dL) and NLR was calculated as neutrophil/lymphocyte ratio. All data were anonymized prior to analysis.

Surgical Approach and Definitions

Indications were categorized as biliary colic, biliary pancreatitis, and acute cholecystitis. The initial surgical approach was laparoscopic.

Difficult cholecystectomy was defined using a composite outcome of any of the following: (i) conversion to open surgery and/or (ii) subtotal (bail-out) cholecystectomy and/or (iii) operative time ≥120 minutes. Operative time has frequently been used as an objective surrogate marker of technical difficulty during laparoscopic cholecystectomy because there is no universal definition of a "difficult" laparoscopic cholecystectomy. Thresholds ranging from 90 to 120 minutes have been adopted in previous studies.[6,7] As our institution is a tertiary referral teaching hospital with resident involvement in surgical training, we selected ≥120 minutes as a conservative and clinically meaningful cut-off to reflect substantial operative prolongation beyond routine cases while minimizing misclassification of moderately extended procedures.

Reasons for conversion were extracted from free-text operative notes and categorized as unsafe/uncertain anatomy, bleeding/hemostasis, biliary tract injury, bowel injury, or other.

Intraoperative complications were recorded. Postoperative complications were graded using the Clavien–Dindo classification.[8,9] Length of hospital stay, ICU requirement, and 30-day mortality were considered secondary outcomes.

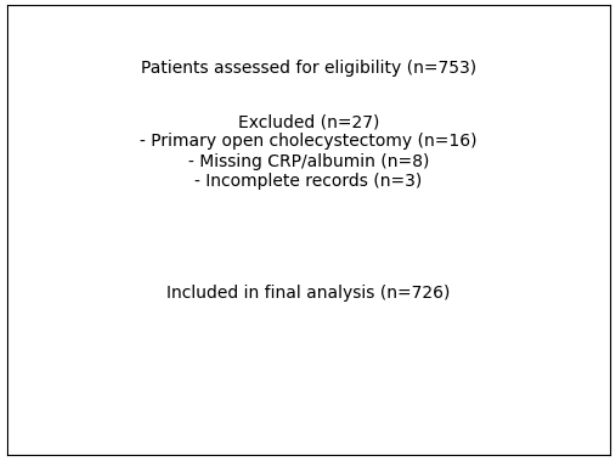

Figure 1. Flow diagram of patient selection and exclusion process

CRP: C-reactive protein

Statistical Analysis

Statistical analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as median [interquartile range, (IQR)], and categorical variables are presented as n (%). Comparisons between difficult and non-difficult groups were conducted using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test, as appropriate, for categorical variables.

A multivariable logistic regression model was built to identify independent factors associated with difficult cholecystectomy. Covariates included age, sex, emergency surgery, acute cholecystitis, ASA ≥III, anticoagulant use, log-transformed CAR (logCAR), and log-transformed NLR. Discrimination was assessed using the area under the receiver operating characteristic curve (ROC) area under the curve (AUC). ROC analyses were performed for CAR, CRP, and NLR, and optimal cut-offs were determined using the Youden index. Statistical significance was set at $p<0.05$.

Ethical Approval

Ethics approval was obtained from the University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital Ethics Committee (approval number: 2025/12-28, date: 05.01.2026). The study was conducted in accordance with the Declaration of Helsinki and its later amendments. Informed consent was waived because the study was retrospective.

RESULTS

A total of 726 patients were included (Table 1). The median age was 70 years (IQR 67–74), and 259/726 (35.7%) were male. Seventy procedures (70/726; 9.6%) were performed under emergency conditions. The indications were biliary colic (642/726; 88.4%), acute cholecystitis (66/726; 9.1%), and biliary pancreatitis (18/726; 2.5%).

Difficult cholecystectomy (conversion, subtotal cholecystectomy, or operative time ≥120 minutes) occurred in 276/726 (38.0%) patients. The conversion rate was 95/726 (13.1%), the subtotal (bail-out) rate was 8/726 (1.1%), and operative time ≥120 minutes occurred in 243/726 (33.5%). Conversion was most commonly due to unsafe or uncertain anatomy (85/95; 89.5%; Table 1).

Compared with the non-difficult group, the difficult group had a higher proportion of males [123/276 (44.6%) vs. 136/450 (30.2%); $p<0.001$], emergency surgery [54/276 (19.6%) vs. 16/450 (3.6%); $p<0.001$], acute cholecystitis as the indication [54/276 (19.6%) vs. 12/450 (2.7%); $p<0.001$], ASA ≥III [82/276 (29.7%) vs. 63/450 (14.0%); $p<0.001$], and anticoagulant use [43/276 (15.6%) vs. 30/450 (6.7%); $p<0.001$] (Table 2). Inflammatory markers were also higher in the difficult group, including CRP [12 (4.5–45) vs. 4.5 (1–12); $p<0.001$] and CAR [3.16 (1.12–12.86) vs. 1.07 (0.26–2.86); $p<0.001$].

Operative time was longer in the difficult group [135 (120–160) vs. 90 (74–99) minutes; $p<0.001$]. Intraoperative complications occurred only in the difficult group [14/276 (5.1%) vs. 0/450 (0.0%); $p<0.001$]. The difficult group also had a longer hospital stay [4 (2–7) vs. 1 (1–2) days; $p<0.001$], a higher ICU requirement [96/276 (34.8%) vs. 38/450 (8.4%); $p<0.001$], and a higher 30-day mortality [8/276 (2.9%) vs. 2/450 (0.4%); $p=0.008$].

In multivariable logistic regression (n=726; AUC =0.727), acute cholecystitis [adjusted odds ratio (aOR) 8.79; 95% confidence interval (CI): 2.00–38.73; $p=0.004$], higher logCAR (aOR 1.45; 95% CI 1.29–1.63; $p<0.001$), and male sex (aOR 1.44; 95% CI 1.02–2.03; $p=0.039$) were independently associated with difficult cholecystectomy (Table 3). The Clavien–Dindo distribution differed between groups (overall $p<0.001$; Table 4), and major complications were more frequent in the difficult group [16/276 (5.8%) vs. 5/450 (1.1%); $p<0.001$].

In ROC analysis, CAR showed modest discrimination in predicting difficult cholecystectomy (AUC 0.700), with an optimal cut-off of 2.75 (sensitivity 55.8%, specificity 74.0%). CRP performed similarly (AUC 0.695; cut-off 9.5 mg/L; sensitivity 58.7%; specificity 70.2%), whereas NLR showed limited discrimination (AUC 0.564).

DISCUSSION

There were two main reasons for centering the study on a laboratory-based approach: First, the technical difficulty during cholecystectomy is largely determined by the severity of inflammation and the resulting edema and fibrosis in Calot's triangle, and this biological burden can be objectively represented by CRP, albumin, and their derived ratios. Secondly, routine biochemistry and hemogram parameters are rapid to obtain, inexpensive, and reproducible, even in emergency situations, and partially offset inter-center variability in clinical evaluations or imaging interpretations. We targeted elderly patients (≥65 years) because comorbidities and decreased physiological reserve are more pronounced in this group, clinical findings are sometimes "subdued," and even minor perioperative stressors can more easily lead to functional decline, complications, and mortality. Therefore, rapid and objective stratification of preoperative risk in the elderly population is increasingly clinically important.[10,11]

Since there is no single universal definition of "DLC" in the literature, we used a clinically significant composite endpoint to increase comparability between studies: conversion and/or subtotal (bail-out) cholecystectomy

Table 1. Baseline characteristics, laboratory parameters, operative details, and outcomes (overall cohort)	
Characteristic	**Overall**
Patients, n	726
Age, years, median (IQR)	70 (67–74)
Male sex, n (%)	259/726 (35.7%)
Urgent surgery, n (%)	70/726 (9.6%)
Indication: biliary colic, n (%)	642/726 (88.4%)
Indication: acute cholecystitis, n (%)	66/726 (9.1%)
Indication: biliary pancreatitis, n (%)	18/726 (2.5%)
ASA I, n (%)	122/726 (16.8%)
ASA II, n (%)	459/726 (63.2%)
ASA III, n (%)	130/726 (17.9%)
ASA IV, n (%)	15/726 (2.1%)
ASA V, n (%)	0/726 (0.0%)
Diabetes mellitus, n (%)	177/726 (24.4%)
Hypertension, n (%)	371/726 (51.1%)
COPD, n (%)	52/726 (7.2%)
Coronary artery disease, n (%)	109/726 (15.0%)
Chronic kidney disease, n (%)	11/726 (1.5%)
Anticoagulant use, n (%)	73/726 (10.1%)
WBC (×10^3/μL), median (IQR)	7.7 (6.4–9.3)
CRP (mg/L), median (IQR)	6 (2.2–20)
Albumin (g/dL), median (IQR)	4 (3.6–4.3)
CAR (CRP/albumin), median (IQR)	1.58 (0.55–5)
NLR (neutrophil/lymphocyte), median (IQR)	2.26 (1.73–3.33)
AST (U/L), median (IQR)	22 (19–30)
ALT (U/L), median (IQR)	19 (15–27)
AST/ALT ratio, median (IQR)	1.11 (0.91–1.39)
GGT (U/L), median (IQR)	32 (20–56)
Total bilirubin (mg/dL), median (IQR)	0.7 (0.54–0.9)
Direct bilirubin (mg/dL), median (IQR)	0.11 (0.09–0.18)
Direct/total bilirubin ratio, median (IQR)	0.17 (0.14–0.22)
Operative time (min), median (IQR)	99 (85–125)
Conversion to open, n (%)	95/726 (13.1%)
Conversion reasons among converted cases	(n=95)
Unsafe/unclear anatomy, n (%)	85/95 (89.5%)
Bleeding/hemostasis, n (%)	2/95 (2.1%)
Bile duct injury, n (%)	4/95 (4.2%)
Bowel injury, n (%)	4/95 (4.2%)
Other/blank, n (%)	0/95 (0.0%)
Subtotal (bail-out) cholecystectomy, n (%)	8/726 (1.1%)
Operative time ≥120 min, n (%)	243/726 (33.5%)
Difficult cholecystectomy (composite)*, n (%)	276/726 (38.0%)
Intraoperative complication, n (%)	14/726 (1.9%)
Intraoperative complication types among complicated cases	(n=14)
Bile duct injury, n (%)	4/14 (28.6%)
Bowel injury, n (%)	9/14 (64.3%)
Bleeding/hemostasis, n (%)	1/14 (7.1%)
Other/blank, n (%)	0/14 (0.0%)
Drain use, n (%)	364/726 (50.1%)
Drain output first 24h (mL), median (IQR)	50 (50–100)
Time to oral intake (hours), median (IQR)	6 (6–6)
Length of stay (days), median (IQR)	2 (1–4)
Any postoperative complication (Clavien–Dindo ≥I), n (%)	60/726 (8.3%)
Major complication (Clavien–Dindo ≥III), n (%)	21/726 (2.9%)

*Difficult cholecystectomy was defined as conversion to open surgery and/or subtotal (bail-out) cholecystectomy and/or operative time ≥120 minutes

IQR: Interquartile range, ASA: American Society of Anesthesiologists, COPD: Chronic obstructive pulmonary disease, WBC: White blood cell, CAR: C-reactive protein-to-albumin, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase

and/or operation time ≥120 min. These three components point to the common ground [advanced inflammation, fibrosis, "frozen Calot", and failure to achieve the critical view of safety (CVS); furthermore, the current safety-focused approach explicitly emphasizes bail-out options such as conversion or subtotal when CVS cannot be achieved, changing strategies, and avoiding insistence when necessary to prevent biliary injury.[1,10] The preference for a composite definition aims to capture clinically critical decisions that might be missed by focusing only on a single endpoint such as "conversion". Current reviews highlight the heterogeneity in the definitions of DLC and the importance of reporting intraoperative endpoints (duration, conversion, complications, etc.) jointly.[6]

In our model, the choice to use logCAR rather than to categorize CAR by a cut-off value is justified by two methodological reasons: (i) CRP and ratio indices generally show a right-skewed distribution in practice; log transformation reduces the influence of outliers and provides a scale more suitable for the model assumptions; (ii) it reduces dependence on a specific threshold choice, producing a more generalizable correlation coefficient across different centers.[12]

Table 2. Comparison of non-difficult vs. difficult cholecystectomy groups (definition: conversion and/or subtotal and/or operative time ≥120 min)

Variable	Non-difficult (n=450)	Difficult (n=276)	p value
Age, years, median (IQR)	70 (67–73)	70 (67–75)	0.047
Male sex, n (%)	136/450 (30.2%)	123/276 (44.6%)	<0.001
Urgent surgery, n (%)	16/450 (3.6%)	54/276 (19.6%)	<0.001
Indication: acute cholecystitis, n (%)	12/450 (2.7%)	54/276 (19.6%)	<0.001
ASA ≥III, n (%)	63/450 (14.0%)	82/276 (29.7%)	<0.001
Anticoagulant use, n (%)	30/450 (6.7%)	43/276 (15.6%)	<0.001
WBC (×10^3/μL), median (IQR)	7.5 (6.3–9.1)	7.9 (6.5–10.2)	0.010
CRP (mg/L), median (IQR)	4.5 (1–12)	12 (4.5–45)	<0.001
Albumin (g/dL), median (IQR)	4.1 (3.8–4.4)	3.8 (3.1–4.3)	<0.001
CAR (CRP/albumin), median (IQR)	1.07 (0.26–2.86)	3.16 (1.12–12.86)	<0.001
NLR (neutrophil/lymphocyte), median (IQR)	2.17 (1.72–3.12)	2.42 (1.74–4.33)	0.003
AST (U/L), median (IQR)	22 (19–30)	23 (19–33)	0.063
ALT (U/L), median (IQR)	19 (15–26)	20 (16–28)	0.055
AST/ALT ratio, median (IQR)	1.11 (0.91–1.4)	1.11 (0.93–1.38)	0.933
GGT (U/L), median (IQR)	28 (18–44)	36 (22–78)	<0.001
Total bilirubin (mg/dL), median (IQR)	0.68 (0.5–0.9)	0.73 (0.59–1.05)	<0.001
Direct bilirubin (mg/dL), median (IQR)	0.1 (0.08–0.16)	0.13 (0.1–0.22)	<0.001
Direct/total bilirubin ratio, median (IQR)	0.17 (0.14–0.2)	0.2 (0.16–0.25)	<0.001
Operative time (min), median (IQR)	90 (74–99)	135 (120–160)	<0.001
Intraoperative complication, n (%)	0/450 (0.0%)	14/276 (5.1%)	<0.001
Length of stay (days), median (IQR)	1 (1–2)	4 (2–7)	<0.001
ICU requirement, n (%)	38/450 (8.4%)	96/276 (34.8%)	<0.001
30-day mortality, n (%)	2/450 (0.4%)	8/276 (2.9%)	0.008

IQR: Interquartile range, ASA: American Society of Anesthesiologists, WBC: White blood cell, CAR: C-reactive protein-to-albumin, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, ICU: Intensive care unit

Table 3. Multivariable logistic regression for predictors of difficult cholecystectomy

Variable	Adjusted OR (95% CI)	p value
Age (per year)	0.98 (0.95–1.01)	0.269
Male sex	1.44 (1.02–2.03)	0.039
Urgent surgery	0.37 (0.08–1.63)	0.187
Acute cholecystitis	8.79 (2.00–38.73)	0.004
ASA ≥III	1.34 (0.85–2.12)	0.207
Anticoagulant use	1.61 (0.89–2.92)	0.117
logCAR	1.45 (1.29–1.63)	<0.001
logNLR	0.86 (0.64–1.16)	0.321
Model performance	n=726, AUC =0.727	

ASA: American Society of Anesthesiologists, OR: Odds ratio, CI: Confidence interval, AUC: Area under the curve, logCAR: log-transformed CAR, logNLR: log-transformed NLR

In our study, the difficult cholecystectomy phenotype was associated not only with prolonged operation time and "bail-out/conversion" but also with worse clinical outcomes, including increased intraoperative complications, longer length of stay, greater ICU requirement, and higher 30-day mortality. This finding suggests that, among older adults, technical difficulty may cease to be a "purely surgical issue" and instead become a risk indicator reflected in outcomes when combined with physiological fragility. Current systematic reviews and meta-analyses have shown frailty to be a significant predictor of adverse outcomes after cholecystectomy in elderly patients.[11]

The finding that acute cholecystitis, male gender, and logCAR remain independent predictors in multivariate analysis is consistent with the literature. The Tokyo approach emphasizes that inflammation in acute cholecystitis complicates anatomical dissection, and that a change in strategy should be implemented at a low threshold if safe technical steps (especially CVS) cannot be achieved.[10]

Table 4. Postoperative complications by Clavien-Dindo grade, stratified by difficulty			
Clavien–Dindo grade	**Non-difficult (n=450)**	**Difficult (n=276)**	**p value**
0	429/450 (95.3%)	221/276 (80.1%)	
I	4/450 (0.9%)	15/276 (5.4%)	
II	12/450 (2.7%)	24/276 (8.7%)	
IIIA	1/450 (0.2%)	5/276 (1.8%)	
IIIB	3/450 (0.7%)	3/276 (1.1%)	
IVA	0/450 (0.0%)	0/276 (0.0%)	
IVB	0/450 (0.0%)	0/276 (0.0%)	
V	1/450 (0.2%)	8/276 (2.9%)	
Overall p value (χ^2) for grade distribution			<0.001
Major complications (≥III) p value			<0.001

The association of male gender with surgical difficulty and conversion has also been identified as a risk factor in previous meta-analyses. Similarly, it has been reported that factors such as acute cholecystitis and age can increase the likelihood of conversion.[7,13]

The emergence of CAR as an independent predictor is biologically consistent with its composite nature, combining inflammatory burden (CRP) and physiological reserve status (albumin) under the same umbrella. Beyond acute cholecystitis, the CAR has been widely investigated as a prognostic biomarker in hospitalized older adults, in inflammatory conditions such as acute pancreatitis, and in gastrointestinal malignancies; in these contexts, elevated CAR has been associated with adverse clinical outcomes and reduced survival.[14-16] Studies have reported that CAR can predict DLC and/or conversion in series of patients with acute cholecystitis defined according to the Tokyo Guidelines 2018 criteria.[4] Although NLR can be associated with "difficulty" in some studies, its effect may not always remain independent in multivariate models because NLR may partly share the same biology as CAR on the inflammatory axis, and in the elderly population, immunosenescence, comorbidity, and drug effects may alter lymphocyte dynamics, reducing specificity. This heterogeneity is consistent with the broader evidence in the DLC literature, which shows that predictors can vary depending on center, recognition, and patient selection.[6,7,13,17]

One of our secondary findings is that laboratory parameters associated with cholestasis, especially Gamma-glutamyl transferase (GGT) and bilirubin fractions, are elevated in difficult cases. This situation can be explained by mechanisms within the clinical spectrum, such as transient obstruction accompanied by acute inflammation, microlithiasis, stone passage, or concomitant choledochal stones. However, the relationship may vary between centers, and cholestasis parameters alone may not clearly represent surgical difficulty. The association of high GGT/ALP and direct bilirubin levels with the need for conversion, reported in some studies, supports our finding.[18] On the other hand, because derived ratios such as the direct/total bilirubin ratio are not widely accepted as established predictors in the literature on DLC, we report them as exploratory findings and do not propose generalizable thresholds.

In our cohort, the aspartate aminotransferase/alanine aminotransferase (De Ritis) ratio did not differ between difficult and non-difficult cases, suggesting limited utility for predicting operative difficulty in this setting. More broadly, the evidence base for the De Ritis ratio regarding prognosis or surgical difficulty in acute cholecystitis remains limited, with heterogeneous results reported.[19] Accordingly, we present this parameter as a secondary observation rather than a primary predictor.

The fact that the vast majority of conversions occur due to "unsafe/uncertain anatomy" is consistent with current safety culture. Multi-association "safe cholecystectomy" guidelines published under the leadership of SAGES emphasize that strategies such as not insisting when CVS cannot be obtained, creating an appropriate dissection window, calling for help, and bail-out procedures (including subtotal cholecystectomy) or conversion when necessary are fundamental in preventing biliary injury.[1] Furthermore, recent studies comparing the outcomes of subtotal cholecystectomy with conversion in difficult cases show that the "bail-out" strategy should be evaluated in the context of patient selection and surgeon experience.[20] The negative impact of difficult cases on clinical outcomes in our cohort supports the value of proactive planning (senior surgeon, appropriate timing, equipment, low-threshold bail-out) in the combination of "risky patient + risky surgical site" in elderly patients.

Study Limitations

The retrospective, single-center design makes it difficult to fully control for confounders such as surgeon experience, surgical timing, details of imaging findings, and selection bias. An important characteristic of our cohort is the predominance of biliary colic cases and the relatively low proportion of acute cholecystitis. Because inflammatory burden is generally higher in acute cholecystitis, the predictive performance of CAR may vary between centers with differing proportions of acute inflammatory cases. Therefore, caution is warranted when extrapolating our findings, and external validation in cohorts enriched with acute cholecystitis is recommended. For DLC, although the composite definition is clinically significant, heterogeneity in definitions persists in the literature; this may affect external validity.[6] The lack of frailty measures (e.g., CFS) and functional outcomes in the elderly population is also a significant limitation, as frailty has been strongly shown to predict morbidity/mortality after cholecystectomy.[9] Finally, although laboratory markers reflect inflammatory biology, choledochal stones, concomitant hepatobiliary pathologies, or comorbid conditions (e.g., chronic liver disease) may affect these markers; therefore, prospective multicenter validation studies are needed.

CONCLUSION

Difficult cholecystectomy phenotype in patients ≥65 years of age is associated with clinically significant poor outcomes. The identification of CAR, using log-transformed analysis, as an independent predictor, along with acute cholecystitis and male gender, supports a practical laboratory-based approach to preoperative risk stratification. This risk stratification, when combined with safety-focused surgical strategies and low-threshold bail-out or conversion decisions, helps reduce complications in elderly patients.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital Ethics Committee (approval number: 2025/12-28, date: 05.01.2026). The study was conducted in accordance with the Declaration of Helsinki and its later amendments.

Informed Consent: Informed consent was waived because the study was retrospective.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.B.N., F.Di., B.G., Concept: O.B.N., F.D., Design: O.B.N., F.D., B.G., Data Collection or Processing: O.B.N., F.D., F.Di., B.G., Analysis or Interpretation: O.B.N., F.Di., B.G., Literature Search: O.B.N., F.D., F.Di., B.G., Writing: O.B.N., F.D., F.Di.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Brunt LM, Deziel DJ, Telem DA, et al; Prevention of Bile Duct Injury Consensus Work Group. Safe cholecystectomy multi-society practice guideline and state-of-the-art consensus conference on prevention of bile duct injury during cholecystectomy. Surg Endosc. 2020;34:2827-55.
2. Pisano M, Allievi N, Gurusamy K, et al. 2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis. World J Emerg Surg. 2020;15:61.
3. Okamoto K, Suzuki K, Takada T, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25:55-72. Erratum in: J Hepatobiliary Pancreat Sci. 2019;26:534.
4. Utsumi M, Sakurai Y, Narusaka T, et al. C-reactive protein to albumin ratio predicts difficult laparoscopic cholecystectomy in patients with acute cholecystitis diagnosed according to the Tokyo Guidelines 2018. Asian J Endosc Surg. 2022;15:487-94.
5. Lee SK, Lee SC, Park JW, Kim SJ. The utility of the preoperative neutrophil-to-lymphocyte ratio in predicting severe cholecystitis: a retrospective cohort study. BMC Surg. 2014;14:100.
6. Abdallah HS, Sedky MH, Sedky ZH. The difficult laparoscopic cholecystectomy: a narrative review. BMC Surg. 20250;25:156.
7. Magnano San Lio R, Barchitta M, Maugeri A, Quartarone S, Basile G, Agodi A. Preoperative risk factors for conversion from laparoscopic to open cholecystectomy: a systematic review and meta-analysis. Int J Environ Res Public Health. 2022;20:408.
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.
9. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187-96.
10. Wakabayashi G, Iwashita Y, Hibi T, et al. Tokyo Guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018;25:73-86.
11. Niknami M, Tahmasbi H, Firouzabadi SR, et al. Frailty as a predictor of mortality and morbidity after cholecystectomy: a systematic review and meta-analysis of cohort studies. Langenbecks Arch Surg. 2024;409:352.
12. Grund B, Sabin C. Analysis of biomarker data: logs, odds ratios, and receiver operating characteristic curves. Curr Opin HIV AIDS. 2010;5:473-9.
13. Wevers KP, van Westreenen HL, Patijn GA. Laparoscopic cholecystectomy in acute cholecystitis: C-reactive protein level combined with age predicts conversion. Surg Laparosc Endosc Percutan Tech. 2013;23:163-6.
14. Ranzani OT, Zampieri FG, Forte DN, Azevedo LC, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One. 2013;8:e59321.

15. Kaplan M, Ates I, Akpinar MY, et al. Predictive value of C-reactive protein/albumin ratio in acute pancreatitis. Hepatobiliary Pancreat Dis Int. 2017;16:424-30.
16. Kinoshita A, Onoda H, Imai N, et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. Ann Surg Oncol. 2015;22:803-10.
17. Wei HH, Wang YX, Xu B, Zhang YG. Preoperative systemic and local inflammation are independent risk factors for difficult laparoscopic cholecystectomy after percutaneous transhepatic gallbladder drainage. Heliyon. 2024;10:e36081.
18. Özdemir A, Karakaya A, Pergel A. Conversion from laparoscopic cholecystectomy to open surgery: reasons and possible risks: a single center experience. Deneysel ve Klinik Tip Dergisi. 2022;39:781-5.
19. Gürlevik E, Akça HŞ, Akça MT, Akça H. The role of the De Ritis ratio in acute cholecystitis: a retrospective observational study. J Contemp Med. 2023;13:388-95.
20. Ramírez-Giraldo C, Monroy DC, Isaza-Restrepo A, et al. Subtotal laparoscopic cholecystectomy versus conversion to open as a bailout procedure: a cohort study. Surg Endosc. 2024;38:4965-75.