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Administrative Office

Chief Physician's Office, Buca Seyfi Demirsoy Training and Research Hospital, Buca/İzmir, Türkiye

Tel: +90 (232) 452 52 52 /4293 **E-mail:** forbestipdergisi@gmail.com

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Editorial

Dear Readers,

As the editorial board of Forbes Journal of Medicine, we are delighted to present the 2026 editorial of our journal with increasing excitement and motivation after our sixth year of publication. In the past year, a total of 39 scientific studies were published in our journal in the fields of Medicine and Health Sciences, including 3 review articles, 34 original research articles, and 2 case reports. As a result of the publication evaluation and printing processes meticulously carried out by the Forbes Journal of Medicine Editorial Board since the first issue, our journal continues to be indexed in our national index ULAKBİM (TR Dizin), Turkish Citation Index, and Turkish Medline, which have a very important place in academic publishing, as well as in international academic indexes such as EBSCO, J-Gate, GALE, and DOAJ. In addition, as of the past year, our journal has also taken its place in the prestigious international indexes Embase, EmCare, and EmBiology. We would like to share that, in line with our goal of further strengthening our journal and achieving success, especially internationally, we are continuing our application process to important international indexes, primarily ESCI and SCOPUS.

As Forbes Journal of Medicine, we closely follow current developments in scientific publication processes, and in this regard, we would like to share that as of the 2026 publication year, our journal will be published only in English and will have transitioned to a continuous publication model. We would like to express our sincere gratitude to the authors who submitted their work to our journal, to the editors and advisory board members who evaluated them, and to our reviewers.

Sincerely,

Professor M. Yekta ÖNCEL, MD
Editor in Chief
Forbes Journal of Medicine

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Original Article

Prognostic Significance of Immune-Inflammation Markers, Lodds and LNR in Locally Advanced Gastric Cancer

Melis KILINÇ[1], Mehmet UZUN[2], İlkay Tuğba ÜNEK[3]

[1]Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, İzmir, Türkiye
[2]University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Division of Medical Oncology, Clinic of Internal Medicine, İzmir, Türkiye
[3]Dokuz Eylül University Faculty of Medicine, Division of Medical Oncology, Department of Internal Medicine, İzmir, Türkiye

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ABSTRACT

Objective: Gastric cancer continues to be a pressing issue in global health. This research seeks to examine the relationship between immune system-related inflammatory markers.

Methods: The research involved 184 cases of locally advanced gastric cancer diagnosed between January 2010 and January 2021. In light of its retrospective methodology, the study did not necessitate informed consent, as per institutional ethical guidelines. Receiver operating characteristic analysis was applied to establish the optimal threshold values for the systemic inflammatory response index (SIRI), systemic inflammatory index (SII), prognostic nutritional index (PNI), pan-immune inflammation value (PIV), neutrophil-lymphocyte ratio, lymph node ratio (LNR) and log odds of positive lymph nodes (LODDS). In these groups, survival outcomes were analyzed using the Kaplan-Meier method. The association between mortality and risk factors was assessed using Cox regression analysis. All tests were deemed statistically significant if the $p<0.05$.

Results: The SIRI, SII, PIV, PNI, LNR and LODDS values were shown to be correlated with overall survival (OS) duration ($p<0.05$). Cox regression model with multiple variables identified that PNI was an independent determinant of OS ($p=0.045$).

Conclusion: The conclusions drawn from this research suggest that immune-inflammation markers, along with the LNR and LODDS values of patients with local advanced stage gastric cancer diagnosis may be used as prognostic factors in routine clinical practice. Detection of these immune-inflammation markers, LNR and LODDS values may guide clinicians in prognostic evaluation as well as the creation of personalized treatment approaches.

Keywords: Gastric cancer, LNR, LODDS

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Corresponding Author:
Melis KILINÇ
Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, İzmir, Türkiye
drmeliskilinc@gmail.com
ORCID ID: 0000-0002-4288-9632

INTRODUCTION

Gastric cancer has the 6th-highest incidence after breast, prostate, lung, colorectal, and cervical cancer, according to GLOBOCAN 2022 predictions for global cancer statistics. With respect to mortality, it ranks 7th, with a rate of 6.1% after lung, breast, colorectal, liver, prostate, and cervical cancers.[1] Accumulating evidence indicates that inflammation plays a crucial role in cancer initiation and progression.[2] In recent years, immune-inflammation-based markers for patients with cancer have been developed using laboratory parameters that are readily available in routine clinical practice, and their prognostic significance has been investigated. The systemic inflammatory response index (SIRI), the systemic inflammatory index (SII), the pan-immune inflammation value (PIV), the prognostic nutritional index (PNI), and the neutrophil-lymphocyte ratio (NLR) may be included among these biomarkers.[3-6]

Pathological lymph node (pN) classification is determined by the number of lymph nodes removed during gastrectomy that are found to be metastatic on pathological examination. The need to develop different classification systems has emerged with the aim of increasing the reliability of lymph node staging.[7] The percentage of metastatic lymph nodes relative to the total number of excised lymph nodes,

referred to as the lymph node ratio (LNR), is calculated after surgical resection for locally advanced gastric cancer and serves as a marker of poor prognosis in high-risk patients.[8-10] The LNR classification system has deficiencies: its prognostic estimation power has been reported to decrease when LNR is 0 or 1. The classification determined using the log odds of positive lymph nodes (LODDS), known as the LODDS value, was identified as better at determining disease prognosis than pN or LNR classifications in gastric cancer. The LODDS value is calculated as the logarithm of the ratio of (metastatic lymph nodes +0.5) to (negative lymph nodes +0.5), and is a novel prognostic factor.[11-15]

In this study, correlations between the biomarkers SIRI, PIV, NLR, SII, PNI, LNR, and LODDS and prognosis were investigated in patients with locally advanced gastric cancer.

METHODS

Patient Population

From January 2010 to January 2021, the study included 184 patients who were diagnosed with locally advanced-stage gastric cancer and had tests and treatment planned at Dokuz Eylül University, Oncology Clinic; they were aged 18 years or older and had no history of secondary solid or hematological tumors. Our study had a retrospective design, and the clinical information, laboratory and pathology results, and treatments administered to patients were recorded. Overall survival (OS) was defined as the interval from the surgical procedure to death or last follow-up. Locally advanced-stage gastric cancer was defined as cT1b-T4 disease in patients without clinically detectable distant metastasis, with or without lymph node involvement.[16]

Immune-Inflammation Markers

Scores for immune-inflammation-based markers were calculated in accordance with definitions and calculation methods reported in the literature, using patients' hematological and biochemical parameters obtained before treatment. The following formulas were used:

NLR: neutrophil (10^3/μL)/lymphocytes (10^3/μL)

SIRI: [neutrophil (10^3/μL) x monocytes (10^3/μL)]/ lymphocytes (10^3/μL)

PIV: [neutrophil (10^3/μL) x monocytes (10^3/μL) x platelets (10^3/μL)]/lymphocytes (10^3/μL)

SII: [neutrophil (10^3/μL) x platelet (10^3/μL)]/lymphocyte (10^3/μL)

PNI: [albumin(g/dL) x 10] + [lymphocytes (10^3/μL) x 0.005]

To determine cut-off values for SIRI, PIV, NLR, SII, PNI, LNR, and LODDS, receiver operating characteristic (ROC) curve analysis was used, and OS analysis was performed. The analysis results in accordance with the ROC curve determined the mean cut-off values were 1.45 [area under the curve (AUC): 0.574 (95% confidence interval (CI): 0.50-0.64, p=0.04] for SIRI, 391.9 [AUC: 0.567 (95% CI: 0.49-0.63, p=0.06)] for PIV, 2.4 [AUC: 0.603 (95% CI: 0.53-0.67, p=0.004)] for NLR, 637.5 [AUC: 0.593 (95% CI: 0.52-0.66, p=0.01)] for SII, 48 [AUC: 0.606 (95% CI: 0.53-0.67, p=0.003)] for PNI, 0.28 [AUC: 0.731 (95% CI: 0.66-0.79, p<0.001)] for LNR and 0.40 [AUC: 0.740 (95% CI: 0.67-0.80, p<0.001)] for LODDS.

LNR and LODDS Classification

LNR is determined by dividing the number of metastatic lymph nodes by the total number of lymph nodes removed. In addition to cases where LNR is 0 or 1, the LNR value is divided into 5 groups in intervals of 0.1. The LNR classification is LNR 1(LNR =0), LNR 2 (0< LNR ≤0.10), LNR 3 (0.1< LNR ≤0.2), LNR 4 (0.2< LNR ≤0.5) and LNR 5 (LNR >0.5). The LODDS value is determined by calculating the logarithm of the ratio of (metastatic lymph nodes +0.5) to (negative lymph nodes +0.5). The categorization of LODDS classes uses intervals of 0.5 and follows a structure comparable to that of LNR classes. The LODDS classification is LODDS 1(LODDS ≤-1.5), LODDS 2 (<-1.5 LODDS ≤-1), LODDS 3 (<-1 LODDS ≤-0.5), and LODDS 4 (-0.5< LODDS ≤0).

Statistical Analysis

Data were analyzed using SPSS 22.0. After descriptive analysis, the normality of quantitative variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparisons of quantitative variables that did not follow a normal distribution between the mortality and progression groups were performed using the Mann-Whitney U test for independent samples. Comparisons of quantitative variables with a bell-shaped distribution were performed using the Student's t-test. Results are reported as median (range) and mean (standard deviation). Comparisons of categorical variables were performed using Fisher's exact test and the chi-square test. Data are reported as numbers (percentages).

Predictive values of immune-inflammatory markers for mortality and progression/recurrence were determined by analysis of the ROC curve. AUC measurements were determined using the Youden index (YI) for parameters with p value <0.05. For each parameter, the value with the highest YI was determined as the cut-off, and the true positive and true negative rates for these cut-offs were calculated. According to these threshold values, patients

were divided into low- and high-risk groups. Survival analysis for these groups was performed using the Kaplan-Meier method. The log-rank test was used to compare median OS values between different risk groups for each parameter. Identification of factors influencing mortality or progression was performed using Cox regression analysis. Findings are reported with 95% confidence. For all tests, $p<0.05$ was considered statistically significant.

Ethics Committee Approval

The study was completed after receiving approval from the Dokuz Eylül University Non-Interventional Research Ethics Committee (dated 10.05.2023 and numbered 8059-GOA).

RESULTS

Among patients diagnosed with locally advanced gastric cancer, 118 male and 66 female patients were included. The median age of the 184 patients was 61 years (range 23–85). According to the Eastern Cooperative Oncology Group (ECOG) performance classification, 48.9% of patients were categorized as ECOG 0, 38% as ECOG 1, 11.4% as ECOG 2, and 1.6% as ECOG >2. Regarding treatment, 52.2% of patients had neoadjuvant chemotherapy, 91.8% had surgical treatment, and 63% had adjuvant radiotherapy. When pathological subtypes were evaluated, the most frequent subtype was adenocarcinoma (77.2%), followed by signet ring cell carcinoma (15.2%). Table 1 provides the clinical and pathological details of the study cohort; Table 2 provides the laboratory parameters used to calculate the immune-inflammation-based markers.

Table 1. Patient clinical and pathological features

Age median, years (min-max)	**61.0 (23-85)**
Sex, n (%)	
Man	118.0 (64.1)
Woman	66.0 (35.9)
Performance status, n (%)	
ECOG 0	90.0 (48.9)
ECOG 1	70.0 (38.0)
ECOG 2	21.0 (11.4)
ECOG >2	3.0 (1.6)
Comorbid disease, n (%)	
HT	47.0 (25.5)
DM	26.0 (14.1)
CAD	4.0 (2.2)
COPD	18.0 (9.8)
Operation, n (%)	169.0 (91.8)
LNR, n (%)	
LNR 1 (LNR =0)	30.0 (17.9)
LNR 2 (0< LNR ≤0.10)	50.0 (29.8)
LNR 3 (0.1< LNR ≤0.2)	24.0 (14.3)
LNR 4 (0.2< LNR ≤0.5)	45.0 (26.8)
LNR 5 (LNR >0.5)	19.0 (11.3)
LODDS classification, n (%)	
LODDS 1 (LODDS ≤-1.5)	32.0 (18.9)
LODDS 2 (-1.5< LODDS ≤-1)	35.0 (20.7)
LODDS 3 (-1< LODDS ≤-0.5)	43.0 (25.4)
LODDS 4 (-0.5< LODDS ≤0)	59.0 (34.9)
Adjuvant RT, n (%)	116.0 (63)
Neoadjuvant CT, n (%)	96.0 (52.2)
Tumor histopathology, n (%)	
Adenocarcinoma	142.0 (77.2)
Signet ring cell carcinoma	28.0 (15.2)
Other	14.0 (7.6)
LNR, median (min-max)	0.1 (0-1)
LODDS, median (min-max)	-0.8 (-2.1-1.2)

ECOG: Eastern Cooperative Oncology Group, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, LNR: Lymph node ratio, LODDS: Log probability of positive lymph nodes, RT: Radiotherapy, CT: Chemotherapy, min: Minimum, max: Maximum

Table 2. Immune-inflammation markers of patients

Parameter	**Median**	**Min-max**
NEU	4.5	0.9-24.5
LYM	1.8	0.4-4.1
HB	11.6	6.3-16.3
PLT	250.0	99.0-587.0
Albumin	3.8	1.8-4.8
SIRI	1.4	0.1-26.1
PIV	391.9	8.3-5472
NLR	2.4	0.7-36.5
SII	637.5	82.6-8788
PNI	48.0	21.5-59.5

NEU: Neutrophil, LYM: Lymphocyte, HB: Hemoglobin, PLT: Platelets, SIRI: Systemic inflammatory response index, PIV: Pan-immune inflammation value, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, PNI: Prognostic nutritional index, min: Minimum, max: Maximum

The median OS of patients was identified as 35.5±4.6 months. Patients with age under or equal to 61 years had median OS of 44.9±7.8 months, while patients over 61 years of age had median OS of 28.4±4.2 months and a notable statistical variation was detected across the age categories ($p=0.020$).

For patients with SIRI value >1.45, the OS was 44.9±19.6 months, while patients with SIRI ≤1.45 had OS of 27.9±3.2 months and the survival durations between the groups were found to be notable statistical variation ($p=0.009$). Patients with PIV ≤391.9 had OS of 44±8 months, while patients with PIV >391.9 had OS of 28.1±3.2 months and there a notable statistical variation for OS durations across

the PIV risk categories (p=0.048). For cases with NLR >2.4, the OS was 44.0±7.1 months, while cases with NLR ≤2.4 had OS of 29.2±3.5 months and there was no notable statistical variation across the groups (p=0.05). Patients with SII ≤637.5 had median OS of 44.9±8.7 months, while patients with SII >637.5 had median OS of 28.4±2.6 months (p=0.031). Patients with PNI >48 had median OS that was statistically significantly longer compared to patients with PNI ≤48 (44.9±10.0 months and 28.0±4.5 months, respectively, p=0.017). Cases having LNR >0.28 had survival durations that were statistically significantly shorter compared to those with LNR ≤0.28 (p<0.001). For cases having LODDS >-0.40, the survival durations were statistically significantly worse than for those having LODDS ≤-0.40 (p<0.001) (Table 3). According to the results of a multivariable Cox regression model developed using immune-inflammation markers PNI values were independent determinants of OS (p=0.045) (Table 4).

DISCUSSION

In this study, significant correlations were observed between immune-inflammation-based markers (SIRI, PIV, SII, PNI), LNR, and LODDS and OS in patients with locally advanced gastric cancer.

SIRI is an index derived from levels of neutrophils, monocytes, and lymphocytes, reflecting the relationship between inflammatory processes and immune function.

In our study, those with SIRI values >1.45 had a significantly shorter median OS. This finding is consistent with the literature reporting that elevated SIRI is associated with an unfavorable prognosis in gastric cancer. Ren et al.[17] similarly associated higher SIRI values with poor OS; however, they did not find an optimal cut-off value. Another study proved that the SIRI index was an independent determinant in patients with gastric cancer who underwent radical gastrectomy.[18] In the literature, the five-year survival rate for gastric cancer cases with high preoperative NLR has been reported to be considerably shorter than that for

Table 3. Correlation of immune-inflammation markers, LNR and LODDS with overall survival

	Kaplan-meier analysis			Cox regression analysis (univariate)	
Parameter	**Median OS (month)**	**95% CI**	**p**	**HR**	**p**
Age ≤61 years >61 years	 44.9±7.8 28.4±4.2	 29.6-60.1 20.1-36.7	**0.019**	1.6 (1.1-2.3)	**0.020**
Sex Man Woman	 42.8±5.9 33.0±3.3	 31.3-54.3 26.6-39.5	0.868	1.0 (0.7-1.5)	0.868
SIRI ≤1.45 >1.45	 44.9±19.6 27.9±3.2	 6.4-83.3 21.6-34.3	**0.009**	1.7 (1.1-2.5)	**0.010**
PIV ≤391.9 >391.9	 44.0±8.0 28.1±3.2	 28.4-59.6 21.8-34.5	**0.048**	1.5 (1.0-2.2)	0.050
NLR ≤2.4 >2.4	 44.0±7.1 29.2±3.5	 30.1-57.9 22.3-36.2	0.050	1.5 (1.0-2.2)	0.051
SII ≤637.5 >637.5	 44.9±8.7 28.4±2.6	 27.9-61.9 23.4-33.5	**0.031**	1.5 (1.0-2.2)	**0.032**
PNI >48.0 ≤48.0	 44.9±10.0 28.0±4.5	 25.3-64.4 19.1-36.7	**0.017**	1.6 (1.1-2.3)	**0.019**
LNR ≤0.28 >0.28	 103.5±--- 24.4±3.3	 ----- 17.9-30.8	**<0.001**	3.7 (2.4-5.6)	**<0.001**
LODDS ≤-0.40 >-0.40	 103.5±--- 24.4±3.3	 ----- 17.9-30.8	**<0.001**	3.7 (2.4-5.6)	**<0.001**

SIRI: Systemic inflammatory response index, PIV: Pan-immune inflammation value, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, PNI: Prognostic nutritional index, LNR: Lymph node ratio, LODDS: Log probability of positive lymph nodes, CI: Confidence interval, OS: Overall survival, HR: Hazard ratio

Table 4. Cox regression model with multiple variables

	Cox regression model with multiple variables		
	HR	**95% CI**	**p**
SIRI ≤1.45 (92.0) vs. >1.45 (92.0)	2.2	1.0-5.2	0.050
PIV ≤391.9 (92.0) vs. >391.9 (92.0)	0.7	0.3-1.8	0.481
NLR ≤2.4 (92.0) vs. >2.4 (92.0)	0.7	0.3-1.5	0.383
SII ≤637.5 (92.0) vs. >637.5 (92.0)	1.4	0.6-2.8	0.421
PNI >48.0 (92.0) vs. ≤48.0 (91.0)	1.5	1.0-2.3	**0.045**

SIRI: Systemic inflammatory response index, PIV: Pan-immune inflammation value, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, PNI: Prognostic nutritional index, CI: Confidence interval, HR: Hazard ratio

cases with low NLR.[19,20] According to the results of this study, no meaningful relationship was found between NLR and survival (Table 2, p=0.05).

With locally advanced gastric cancer, patients with SII >637.5 had shorter median OS duration compared to patients with SII ≤637.5. In the literature, cases with elevated SII exhibited shorter OS.[21] A study including a broad group of patients found that increased SII prior to surgery is an independent determinant of adverse prognosis in gastric cancer.[20]

In cases with locally advanced gastric cancer, cases with PNI >48 had statistically significantly longer median OS compared to patients with PNI ≤48. In our study, in light of the results from the Cox regression model with multiple variables developed using immune-inflammation markers, cases with a PNI ≤48 demonstrated a substantial increase in mortality (p=0.045). In the literature, increased PNI was associated with longer OS. In these studies, multivariate analyses showed that a low PNI value was an independent determinant of worse OS.[22,23] Identifying PNI as an independent risk factor for OS reiterates the importance of nutritional status for cancer prognosis. Providing nutritional support to patients with gastric cancer in the preoperative period has the potential to improve survival. Additionally, combining PNI with other inflammation markers may be beneficial in creating stronger prognostic models.

In our study, the LNR and LODDS values, which evaluate lymph node metastasis, were correlated with prognosis. In patients having an LNR >0.28, median OS was statistically significantly shorter in comparison to those with an LNR ≤0.28. In the literature, the percentage of lymph nodes involved by metastasis has served as a prognostic indicator, independent of the number of lymph nodes removed during the operation. An increase in this proportion was associated with decreased OS.[24,25] As part of our research, cases with LODDS >-0.40 were found to have statistically significantly shorter median OS relative to cases with LODDS ≤-0.40. Determining pN stages based solely on the lymph node count with metastasis and the classification variation between <15 and ≥15 lymph nodes highlighted the need for stronger prognostic measures, such as LNR and LODDS, to predict outcomes. LODDS accounts for both metastatic and non-metastatic lymph node counts. It was developed to provide an accurate prognostic assessment for patients with pN0 and <15 removed lymph nodes. In the literature, as the LODDS degree increases, prognosis is affected, and LODDS appears to be a more reliable prognostic indicator than pN.[26]

CONCLUSION

Our study demonstrated the usefulness of the immune-inflammation markers LNR and LODDS as prognostic factors in clinical practice for patients with locally advanced gastric cancer. Due to the ease of measurement using routine blood tests and the number of lymph nodes with and without metastasis in pathology reports, they offer practical and economic benefits. Detection of these immune-inflammation markers, LNR and LODDS values, may guide clinicians in predicting patient prognosis and planning optimal treatment.

Ethics

Ethics Committee Approval: The study was completed after receiving approval from the Dokuz Eylül University Non-Interventional Research Ethics Committee (dated 10.05.2023 and numbered 8059-GOA).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K., Concept: M.U., İ.T.Ü., Design: M.U., İ.T.Ü., Data Collection or Processing: M.K., Analysis or Interpretation: M.K., M.U., İ.T.Ü., Literature Search: M.K., Writing: M.K.

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

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Original Article

The Effect of Preoperative Kellgren–Lawrence Grade on Length of Stay and Early Postoperative Complications After Primary Total Knee Arthroplasty

Yılmaz ÖNDER[1], Tolgacan KURTULUŞ[2], Mahmut TUNÇEZ[1], Tuğrul BULUT[1]

[1]İzmir Katip Çelebi University, Atatürk Training and Research Hospital, Department of Orthopaedics and Traumatology, İzmir, Türkiye
[2]University of Health Sciences Türkiye, İzmir City Hospital, Clinic of Orthopaedics and Traumatology, İzmir, Türkiye

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ABSTRACT

Introduction: The aim of this study is to investigate the relationship between preoperative Kellgren–Lawrence (KL) grade and hospital length of stay and early postoperative complications in patients undergoing primary total knee arthroplasty (TKA).

Methods: Patients who underwent cemented posterior-stabilized TKA between January 2023 and January 2026 were retrospectively evaluated. Patients aged ≥55 years with a diagnosis of primary knee osteoarthritis (OA), preoperative weight-bearing knee plain radiographs, and at least 6 months of follow-up were included in the study. Valgus deformity, KL grade 2, body mass index (BMI) ≥35, inflammatory arthritis, post-traumatic arthritis, revision surgery, and patients without adequate follow-up or suitable plain radiographs were excluded. Patients were grouped according to their KL grades. All demographic variables, in addition to hospital length of stay and early minor and major complications, were statistically evaluated. Statistical significance was defined as a p value <0.05 for all analyses.

Results: A total of 482 patients were included in the study (KL grade 3: n=254, 52.7%; KL grade 4: n=228, 47.3%). There were no significant differences between the groups in terms of age, BMI, surgical time, American Society of Anesthesiologists score, Charlson comorbidity index, and blood transfusion requirement (for each p>0.05). Hospital length of stay was significantly longer in the KL grade 4 group (p=0.004). The rate of major complications was higher in the KL grade 4 group (p=0.031), while the rates of minor complications were similar (p>0.05).

Conclusion: Increased preoperative radiographic OA severity is associated with longer hospital length of stay and a higher rate of major complications after primary TKA.

Keywords: Kellgren–Lawrence grade, knee osteoarthritis, total knee arthroplasty, length of stay, early postoperative complication

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Corresponding Author:
Tuğrul BULUT
İzmir Katip Çelebi University, Atatürk Training and Research Hospital, Department of Orthopaedics and Traumatology, İzmir, Türkiye
drtugrulbulut@yahoo.com
ORCID ID: 0000-0002-7075-0873

INTRODUCTION

In knee osteoarthritis (OA), patients' tendency to avoid surgery and their efforts to delay it by resorting to non-surgical alternative treatments can exacerbate limitations in physical activity, potentially increasing the risk of further disability and chronic disease.[1,2] Consequently, total knee arthroplasty (TKA) is often performed at more advanced radiographic stages, particularly in Kellgren–Lawrence (KL) grade 4. When the relevant literature is reviewed, studies comparing patients with advanced-stage KL grades 3 and 4 report that the two groups are often similar with respect to postoperative functional outcomes and patient-reported scores after TKA.[3,4] However, studies evaluating critical outcomes, such as hospital length of stay and early complications, comparing these two grades have been relatively limited.

In KL grade 3 patients, joint deformities and soft tissue contractures are more limited than in KL grade 4 patients. This can affect the level of surgical difficulty, the early postoperative recovery process, and the risk of complications. Therefore, comparing early hospital outcomes in patients with KL grades 3 and 4 is important

clinically and for determining their burden on the healthcare system.

The hypothesis of this study is that patients with KL grade 3 will have a shorter hospital length of stay and lower rates of early postoperative complications compared to patients with KL grade 4.

The aim of this study is to investigate the relationship between preoperative KL grade, hospital length of stay, and early postoperative complication rates in patients undergoing primary TKA.

METHODS

This retrospective study was approved by the İzmir Katip Çelebi University Institutional Review Board (approval number: 0015, date: 15.01.2026). All procedures involving human participants were conducted in accordance with the institutional committee's ethical standards.

Patient Inclusion

In this study, 1057 patients who underwent primary TKA between January 2023 and January 2026 were retrospectively evaluated. Patients who underwent cemented posterior-stabilized TKA for KL grade 3 or 4 primary knee OA; who were ≥55 years of age, had preoperative weight-bearing knee plain radiographs, and had at least 6 months of postoperative follow-up been included in the study. Exclusion criterias for this study were; revision TKA, valgus deformity OA, KL grade 2 OA, body mass index (BMI) ≥35, uncemented or cruciate-retaining TKA, inflammatory arthritis, post-traumatic osteoarthritis, concurrent major joint surgery, tumor or active infection, and lack of suitable radiographs or adequate postoperative follow-up. In total, 482 patients were included in the study (Figure 1).

Surgical Technique and Follow-Up Protocol

All patients underwent surgery under regional anesthesia. A midline skin incision was made with a pneumatic tourniquet, and a medial arthrotomy was performed via a standard medial parapatellar approach. Cemented posterior-stabilized TKA was performed without patellar resurfacing. The hemovac drain was removed on the first postoperative day. Mobilization and active range-of-motion exercises were initiated with full weight-bearing, using walking aids. 5000 IU of low-molecular-weight heparin was administered subcutaneously for 30 days as venous thromboembolism prophylaxis. As antibiotic prophylaxis, 1 g of cefazolin was administered intravenously as a single dose before surgery, followed by three doses within the first 16 hours after surgery. Patients were discharged when pain was controlled with oral medication, functional independence was achieved with walking aids, and prolonged wound drainage requiring hospital follow-up was no longer present. Clinical and radiological follow-ups were performed weekly during the first month, monthly for the next 5 months, and quarterly thereafter.

Patient Evaluation

Detailed demographic and clinical data, such as age, gender, BMI, American Society of Anesthesiologists (ASA) score, Charlson comorbidity index (CCI), surgical time, blood transfusion requirement, and hospital length of stay, were recorded for all patients. Minor and major complications developing during follow-up periods of at least 6 months were recorded. Complications were classified as minor or major according to their clinical severity and the level of treatment required. Classification was performed in accordance with widely accepted surgical complication grading systems and the TKA literature.[5-8]

Minor complications were defined as events that could be managed with conservative treatment or medical support without requiring invasive surgery or intensive care. This group included prolonged serous wound drainage (discharge lasting longer than 72 hours and causing more than 2x2 cm of wetting in the dressing), superficial wound infection (limited to the skin and subcutaneous tissue and resolving with antibiotic treatment), hematoma or seroma (not requiring surgical drainage), limitation of range of motion (ROM), urinary retention or urinary tract infection, electrolyte imbalances, and transient gastrointestinal complications.

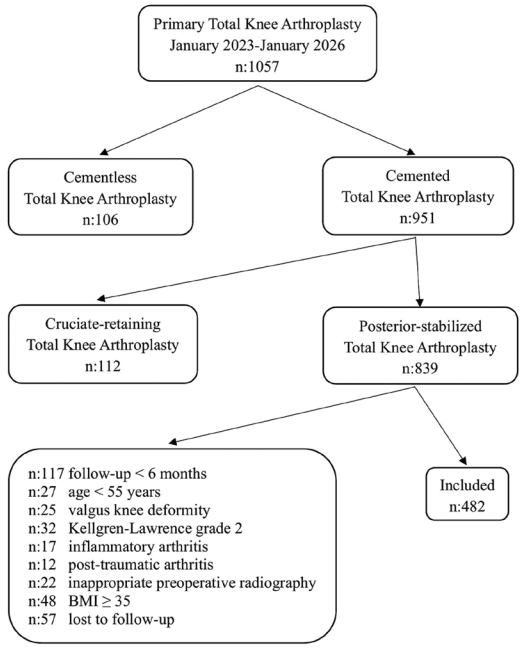

Figure 1. Patient flowchart of the study

BMI: Body mass index

Major complications were defined as life-threatening events requiring surgical, endoscopic, or interventional treatment; requiring intensive care monitoring; or associated with permanent morbidity or mortality. This group included the following: periprosthetic joint infection (requiring surgical debridement, component exchange, or revision); superficial wound necrosis (requiring debridement); intraoperative vascular, nerve, or ligament injuries; venous thromboembolism (deep vein thrombosis or pulmonary embolism); major cardiovascular diseases (myocardial infarction, stroke); acute renal failure; sepsis or septic shock; periprosthetic fractures; complications requiring reoperation such as dislocation; and postoperative mortality.

Radiographic Evaluation

Radiological assessments were performed digitally using the picture archiving and communication system. All patients were evaluated according to the KL grading system using preoperative weight-bearing anteroposterior and lateral plain radiographs of the knee.[9] The presence of numerous osteophytes, significant joint space narrowing, sclerosis, and possible bone deformity was classified as KL grade 3 (Figure 2). Large osteophytes, significant joint space narrowing, severe sclerosis, and definite bone deformity were classified as KL grade 4 (Figure 3). All evaluations were conducted by two independent observers — one orthopedic specialist and one radiologist — and decisions were reached by consensus.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics Standard Concurrent User V 22 (IBM Corp, Armonk, New York, USA) statistical software package. Descriptive statistics were presented as number of units (n), percentage (%), mean ± standard deviation ($\bar{x}$ ± SD), median, minimum, and maximum (max) values. Normality of the numerical variables was assessed using the Kolmogorov-Smirnov test. The numerical variables did not conform to the assumption of normality. The Mann-Whitney U test was used to compare numerical variables among KL grade groups. The Pearson chi-square test was used to compare categorical variables across KL grades. The statistical significance level was set at $p<0.05$.

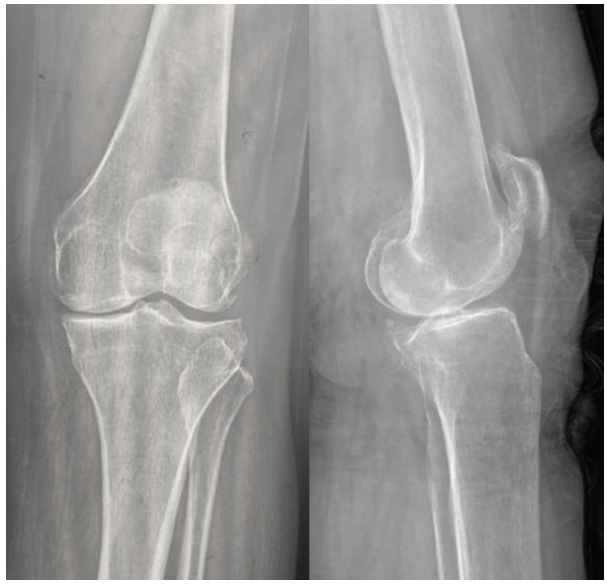

Figure 2. Weight-bearing anteroposterior and lateral knee plain radiographs of a 62-year-old female patient with Kellgren–Lawrence grade 3 knee osteoarthritis

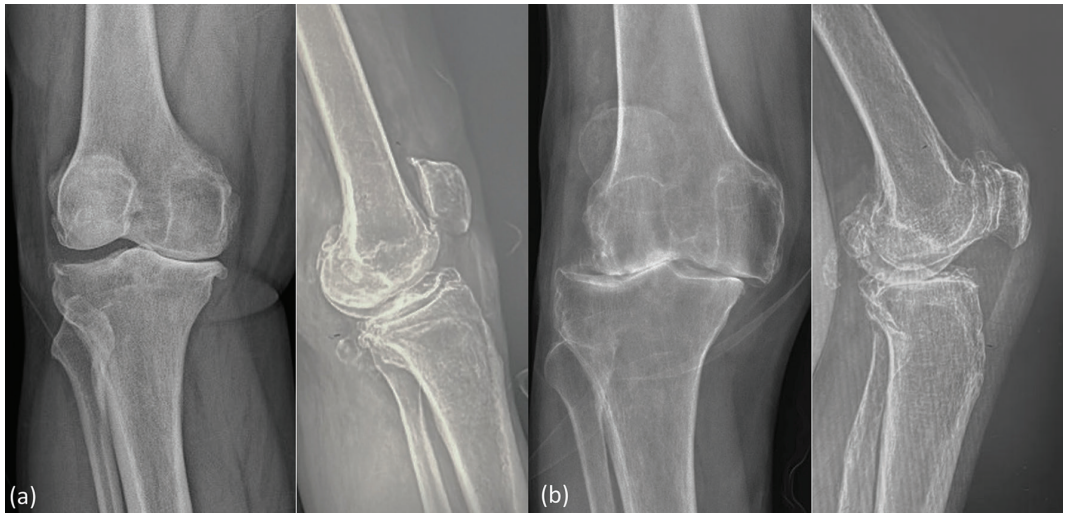

Figure 3. Weight-bearing anteroposterior and lateral knee radiographs of Kellgren–Lawrence grade 4 knee osteoarthritis: (a) 65-year-old female patient; (b) 68-year-old female patient. Significant joint deformity and flexion contracture are observed in (b)

RESULTS

The study included 254 patients with KL grade 3 (52.7%) and 228 patients with KL grade 4 (47.3%). Three hundred and ninety-eight (82.6%) of the patients were female and 84 (17.4%) were male. When all patients were evaluated, the mean age was 67.7±6.7 years, the mean follow-up was 19.4±8.7 months, the mean BMI was 26.6±2.0 kg/m², the mean surgical time was 100.5±24.6 minutes, and the mean hospital length of stay was 5.8±2.2 days. The mean transfusion amount in patients who received blood transfusions was 1.9±0.9 units. When complications were evaluated, no systemic complications affecting major organ systems were detected in any patient. Minor complications were observed in 48 patients (10.0%), and major complications in 54 patients (11.2%) (Table 1).

Prolonged wound drainage developed in 18 patients (3.7%). These cases were managed without surgery by temporarily discontinuing prophylactic low-molecular-weight heparin and repeating dressing changes. Superficial wound infection occurred in 20 patients (4.2%) and was successfully treated with oral antibiotic therapy and local wound care. Eight hematomas (1.7%) that developed in the postoperative period were managed conservatively by aspiration. Two patients (0.4%) experienced a postoperative restricted ROM. One of these patients showed clinical improvement with physical therapy, whereas the other did not. In this case, a 10° extension restriction developed during follow-up, and max knee flexion was limited to 90° (Table 2).

Among major complications, deep vein thrombosis developed in 1 patient (0.2%) and was successfully managed with medical treatment. Intraoperative medial collateral ligament injury was detected in 4 patients (0.8%); these cases were successfully treated with primary repair using screw suture anchors and knee brace immobilization for 6 weeks. In 2 patients (0.4%), surgical debridement was performed because of superficial wound necrosis, and negative-pressure wound therapy, also known as vacuum-assisted closure, was used to promote wound healing. One patient (0.2%) experienced a dislocation following a fall down the stairs during the postoperative period and underwent revision surgery. Additionally, one patient (0.2%) developed an intraoperative tibial periprosthetic fracture; internal fixation was achieved in the same surgical session. Regarding infectious complications, 29 cases (6.0%) that developed early acute infection were treated with debridement, antibiotics, and implant retention with exchange of the polyethylene insert. One patient (0.2%) underwent one-stage revision arthroplasty due to an infection that developed during the second postoperative month. Two-stage revision arthroplasty was performed in 15 patients (3.2%) (Table 2).

No statistically significant differences were found between the groups included in the study with respect to age, gender, follow-up, side (right/left), blood transfusion, surgical time, BMI, ASA score, CCI, and presence of minor complications (for each $p>0.05$) (Table 3).

The presence of major complications differed significantly across KL grades ($p=0.031$). It was found that patients in KL grade 4 developed major complications more frequently than those in KL grade 3. In addition, hospital length of stay showed a statistically significant difference between KL grades ($p=0.004$). It was found that the hospital length of stay was longer in KL grade 4 patients compared to KL grade 3 patients (6.1±2.7 days; 5.5±1.6 days, respectively) (Table 3).

Table 1. Descriptive variables of patients

Variables	n	%
Sex		
Female	398	82.6
Male	84	17.4
Side		
Right	233	48.3
Left	249	51.7
ASA score		
1	11	2.2
2	374	77.5
3	97	20.3
CCI		
0-2	57	11.8
3-4	280	58.1
≥5	145	30.1
KL grade		
3	254	52.7
4	228	47.3

Table 1. Continued		
Variables	**n**	**%**
Blood transfusion		
Negative	180	37.3
Positive	302	62.7
Blood transfusion (unit)		
0	180	37.3
1	124	25.7
2	123	25.5
3	38	7.9
4	10	2.1
5	7	1.5
Minor complication		
Negative	434	90.0
Positive	48	10.0
Major complication		
Negative	428	88.8
Positive	54	11.2
	$\bar{x}$ ± SD	**M (min-max)**
Age (year)	67.7±6.7	68.0 (55.0-87.0)
Follow-up (month)	19.4±8.7	18.4 (6.3-36.2)
BMI	26.6±2.0	27.0 (21.0-34.0)
Surgical time (minute)	100.5±24.6	100.0 (40.0-190.0)
Length of stay (day)	5.8±2.2	5.0 (3.0-27.0)
Blood transfusion (unit)	1.9±0.9	2.0 (1.0-5.0)

n: Number of patients, %: Column percentage, $\bar{x}$ ± SD: Mean ± standard deviation, M: Median, min: Minimum, max: Maximum, BMI: Body mass index, ASA: American Society of Anesthesiologists, CCI: Charlson comorbidity index, KL: Kellgren–Lawrence

Table 2. Distribution of complications in groups						
	All patients		**KL grade 3**		**KL grade 4**	
	n	**%**	**n**	**%**	**n**	**%**
Minor complication	48	10.0	23	9.0	25	11.0
Prolonged wound drainage	18	3.7	11	4.3	7	3.1
Superficial wound infection	20	4.2	8	3.1	12	5.3
Hematoma	8	1.7	3	1.2	5	2.2
Restricted ROM	2	0.4	1	0.4	1	0.4
Major complication	54	11.2	21	8.3	33	14.5
Superficial wound necrosis	2	0.4	-	-	2	0.9
Infection (DAIR)	29	6.0	12	4.7	17	7.5
Infection (two-stage revision)	15	3.2	5	2.0	10	4.4
Infection (one-stage revision)	1	0.2	1	0.4	-	-
DVT	1	0.2	-	-	1	0.4
Dislocation	1	0.2	-	-	1	0.4
Intraoperative periprosthetic fracture	1	0.2	1	0.4	-	-
Intraoperative MCL injury	4	0.8	2	0.8	2	0.9

KL: Kellgren–Lawrence, ROM: Range of motion, DAIR: Debridement, antibiotic, and implant retention, DVT: Deep vein thrombosis, MCL: Medial collateral ligament

Table 3. Comparison of variables according to groups					
Variables	**KL grade 3**		**KL grade 4**		**p value**
	n	**%**	**n**	**%**	
Sex					
Sex	213	83.9	185	81.1	0.432
Male	41	16.1	43	18.9	
Side					
Right	129	50.8	104	45.6	0.256
Left	125	49.2	124	54.4	
ASA score					
1	8	3.1	3	1.3	0.336
2	170	66.9	176	77.2	
3	76	29.9	49	21.5	
CCI					
0-2	24	9.4	33	14.5	0.152
3-4	147	57.9	133	58.3	
≥5	83	32.7	62	27.2	
Blood transfusion (unit)					
0	96	37.8	84	36.8	0.646
1	68	26.8	56	24.6	
2	59	23.2	64	28.1	
≥3	31	12.2	24	10.5	
Blood transfusion					
Negative	96	37.8	84	36.8	0.829
Positive	158	62.2	144	63.2	
Minor complication					
Negative	231	90.9	203	89.0	0.485
Positive	23	9.1	25	11.0	
Major complication					
Negative	233	91.7	195	85.5	0.031
Positive	21	8.3	33	14.5	
	$\bar{x}$ ± SD	**M (min-max)**	**$\bar{x}$ ± SD**	**M (min-max)**	
Age (year)	67.8±6.6	68.0 (56.0-85.0)	67.7±6.9	68.0 (55.0-87.0)	0.830
Follow-up (month)	19.0±9.4	16.9 (6.3-36.2)	19.9±7.8	19.5 (6.5-35.9)	0.105
BMI	26.7±2.0	27.0 (21.0-34.0)	26.5±2.0	27.0 (21.0-29.0)	0.592
Surgical time (minute)	99.7±26.8	100.0 (40.0-190.0)	101.3±22.0	105.0 (45.0-160.0)	0.202
Length of stay (day)	5.5±1.6	5.0 (3.0-15.0)	6.1±2.7	5.0 (3.0-27.0)	0.004
Blood transfusion (unit)	1.9±1.0	2.0 (1.0-5.0)	1.8±0.8	2.0 (1.0-5.0)	0.820

KL: Kellgren–Lawrence, n: Number of patients, %: Column percentage, ASA: American Society of Anesthesiologists, CCI: Charlson comorbidity index. $\bar{x}$ ± SD: Mean ± standard deviation, M: median, min: Minimum, max: Maximum, BMI: Body mass index

DISCUSSION

The results demonstrated that the preoperative radiographic severity of OA in patients undergoing primary TKA was significantly associated with length of hospital stay and early postoperative complications. Hospital length of stay was longer in KL grade 4 patients, and the rate of early-period major complications was significantly higher than that in KL grade 3 patients. One possible explanation for this relationship is that the KL classification exhibits a pronounced ceiling effect in advanced knee OA and does not provide sufficient detail for severe cases. KL grade 4 defines advanced disease, in which the joint space is completely lost; however, it does not sufficiently differentiate among parameters such as the degree of deformity, bone loss, osteophyte burden, and soft-tissue contracture, which can directly affect surgical difficulty and early rehabilitation. Therefore, it is possible for a patient with a completely closed joint space but minimal deformity to be assigned the same grade (KL 4) as a patient with advanced deformity and severe contracture. Keenan et al.[10] have highlighted the limited discriminatory power of the KL grading system in advanced OA. Although the degrees of deformity and soft tissue contracture were not objectively measured in our study, it is likely that cases with more complex deformities and contractures were relatively more prevalent in the KL grade 4 group. In this patient group, more challenging surgical exposure, increased need for ligament balancing, and delayed postoperative rehabilitation may be associated with prolonged hospital stay and increased risk of early postoperative complications.

The observation that KL grade 4 patients had longer hospital stays in our study is an important finding with significant implications for healthcare resource utilisation and costs. A review of the relevant literature shows that prolonged hospital stay is associated with increased rates of complications and readmissions following joint arthroplasty.[10-13] The most important reasons for this are the frequent occurrence of marked joint deformities, widespread osteophyte formation, subchondral bone changes, and capsular contractures in KL grade 4 knee OA. These structural changes can make the surgical procedure more complex from a technical point of view. As a result, postoperative pain control may become more difficult, and early mobilisation may be delayed. The time to achieve functional independence may be prolonged. Consequently, an increase in hospital length of stay may be anticipated. None of the patients in our study experienced complications that prolonged length of hospital stay, except for prolonged wound drainage. All complications, except for medial collateral ligament injury and periprosthetic fracture, developed after discharge. Considering that prolonged wound drainage is a minor complication treated conservatively, the degree of OA is responsible for the longer hospital stay.

Another important finding was that the rate of early major complications was significantly higher among patients with KL grade 4. We believe that there are two reasons for this. The expected progression of OA to the final radiographic grade may increase joint deformity and capsular contracture, thereby making surgery more difficult. Second, in advanced OA, the decline in joint-related functional capacity and lower-extremity muscle strength may lead to deterioration in patients' overall health, making them more susceptible to complications. Indeed, studies have shown that advanced knee OA is associated with frailty syndrome, characterised by a decline in physical reserves and reduced physiological resilience to stress, and may increase frailty.[14] Although traditional risk classification systems such as ASA and CCI reflect the general health status of patients, an advanced radiographic stage of OA may increase the risk of early complications independent of the burden of systemic comorbidity. It should be borne in mind that these indices, which are frequently used in clinical practice, may not be sufficient on their own to predict the risk of early postoperative complications after TKA.

In recent years, insurance companies in many developed countries, particularly the United States, have introduced pre-authorisation criteria for TKA and restricted surgery to patients with KL grade 4 OA.[4] This approach is based on the assumption that the clinical benefit of surgery may be lower for patients with early-grade OA.[15,16] However, our study shows that delaying surgery until the radiographic end-stage may create disadvantages in terms of hospital length of stay and early major complications. The KL classification system cannot clearly distinguish the severity within advanced OA. Therefore, we believe that radiographic grade should not be the sole criterion for surgical decision-making. This approach may lead to the postponement of definitive treatment, particularly in symptomatic KL grade 3 patients. This is an important parameter that may affect early hospital-based outcomes. Our study shows that preoperative radiographic OA severity is associated with early hospital-based outcomes after primary TKA. Longer hospital stays and higher rates of early-period major complications have been observed among KL grade 4 patients. These findings suggest that an advanced radiographic stage may be a clinical indicator affecting not only disease severity but also the early postoperative recovery process and hospital resource utilisation.

This study has some limitations. The retrospective design precludes establishing causal relationships, and unmeasured confounding variables may have influenced the results. The lack of patient-reported outcome measures and long-term functional outcome assessments limits the study to early hospital-based outcomes. Furthermore, the lack of assessment of the inter- and intra-observer reliability of radiographic evaluations may increase the risk of observer bias. Nevertheless, the analysis of a large patient cohort, a homogeneous surgical procedure, and standardised early-period outcomes is among the strengths of this study.

CONCLUSION

This study demonstrates that the preoperative KL grade in patients undergoing primary TKA may create clinically significant differences in hospital length of stay and early postoperative major complications. Patients with KL grade 4 OA were found to have longer hospital stays and higher rates of early major complications. These findings suggest that severe radiographic OA may increase surgical complexity and impair early postoperative recovery, independent of systemic comorbidity scores. Prospective, multicentre studies will support the evaluation of advanced-stage OA through the use of more detailed radiographic classifications and the development of clinical decision algorithms for optimal timing of surgery.

Ethics

Ethics Committee Approval: This retrospective study was approved by the İzmir Katip Çelebi University Institutional Review Board (approval number: 0015, date: 15.01.2026).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.Ö., M.T., T.K., T.B., Concept: Y.Ö., M.T., T.B., Design: Y.Ö., M.T., T.K., Data Collection or Processing: Y.Ö., T.K., Analysis or Interpretation: Y.Ö., T.B., Literature Search: Y.Ö., T.B., Writing: Y.Ö., M.T., T.B.

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

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

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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

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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

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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.

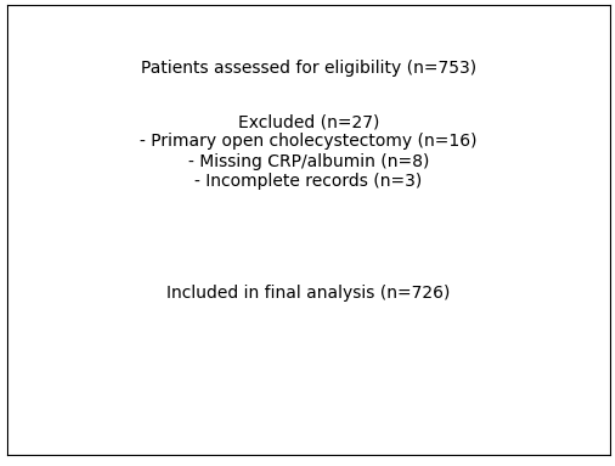

Figure 1. Flow diagram of patient selection and exclusion process

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.

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