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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



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

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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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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 ($10^3/\mu\text{L}$)/lymphocytes ($10^3/\mu\text{L}$)

SIRI: [neutrophil ($10^3/\mu\text{L}$) x monocytes ($10^3/\mu\text{L}$)]/lymphocytes ($10^3/\mu\text{L}$)

PIV: [neutrophil ($10^3/\mu\text{L}$) x monocytes ($10^3/\mu\text{L}$) x platelets ($10^3/\mu\text{L}$)]/lymphocytes ($10^3/\mu\text{L}$)

SII: [neutrophil ($10^3/\mu\text{L}$) x platelet ($10^3/\mu\text{L}$)]/lymphocyte ($10^3/\mu\text{L}$)

PNI: [albumin(g/dL) x 10] + [lymphocytes ($10^3/\mu\text{L}$) 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 ($0 < \text{LNR} \leq 0.10$), LNR 3 ($0.1 < \text{LNR} \leq 0.2$), LNR 4 ($0.2 < \text{LNR} \leq 0.5$) and LNR 5 ($\text{LNR} > 0.5$). 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 ($\text{LODDS} \leq -1.5$), LODDS 2 ($-1.5 < \text{LODDS} \leq -1$), LODDS 3 ($-1 < \text{LODDS} \leq -0.5$), and LODDS 4 ($-0.5 < \text{LODDS} \leq 0$).

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.

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)

Age median, years (min-max)	61.0 (23-85)
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

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 $NLR \leq 2.4$ had OS of 29.2 ± 3.5 months and there was no notable statistical variation across the groups ($p=0.05$). Patients with $SII \leq 637.5$ 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 $PNI \leq 48$ (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 $LNR \leq 0.28$ ($p < 0.001$). For cases having $LODDS > -0.40$, the survival durations were statistically significantly worse than for those having $LODDS \leq -0.40$ ($p < 0.001$) (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

Parameter	Kaplan-meier analysis			Cox regression analysis (univariate)	
	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.

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

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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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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.

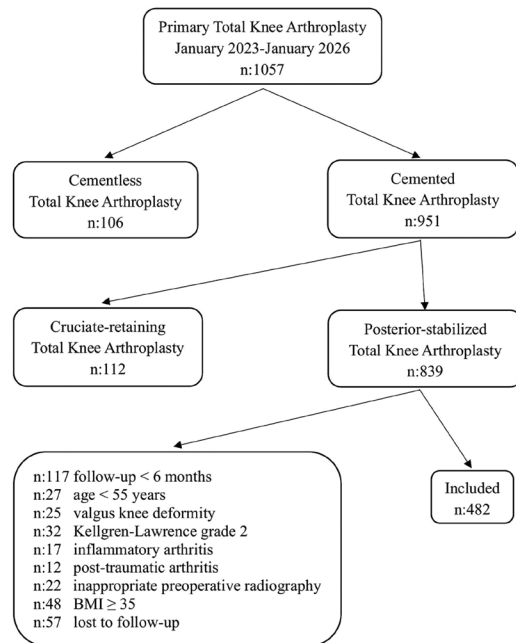


Figure 1. Patient flowchart of the study
BMI: Body mass index

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 \pm standard deviation ($\bar{x} \pm SD$), 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 $p < 0.05$.

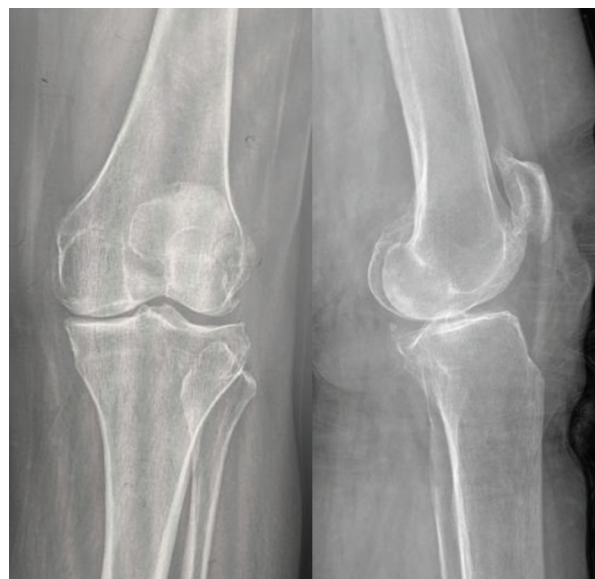


Figure 2. Weight-bearing anteroposterior and lateral knee plain radiographs of a 62-year-old female patient with Kellgren–Lawrence grade 3 knee osteoarthritis



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).

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
	$\bar{x} \pm SD$	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, $\bar{x} \pm SD$: Mean \pm 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						
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						
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	
	$\bar{x} \pm SD$	M (min-max)	$\bar{x} \pm SD$	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. $\bar{x} \pm SD$: 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.

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

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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 (25th–75th 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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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.

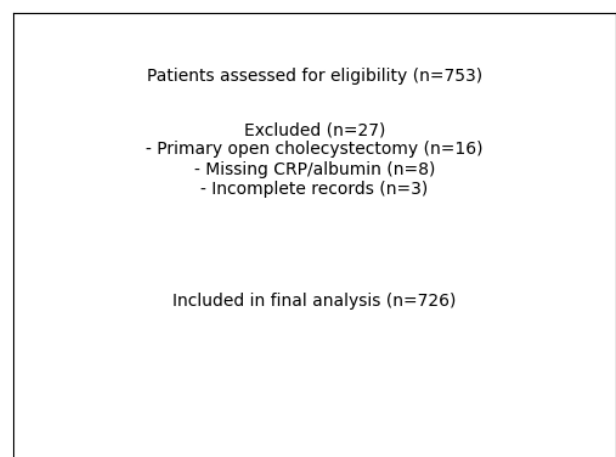


Figure 1. Flow diagram of patient selection and exclusion process

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 \geq 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 \geq 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 \geq 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 \geq 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

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 ($\times 10^3/\mu\text{L}$), 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%)

Characteristic	Overall
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 ≥ 1), n (%)	60/726 (8.3%)
Major complication (Clavien–Dindo ≥ 3), 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

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 (\geq 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.

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Contemporary Outcomes of Chorionic Villus Sampling from the First Trimester to Neonatal Follow-Up

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ABSTRACT

Objective: To evaluate contemporary indications, diagnostic yield, diagnostic limitations, and pregnancy–neonatal outcomes of chorionic villus sampling (CVS) in a tertiary referral population in the era of widespread non-invasive prenatal testing.

Methods: This retrospective cohort study included 70 singleton pregnancies that underwent CVS at a tertiary referral center between October 2023 and June 2025. Maternal characteristics, indications for CVS, genetic testing results, and procedure-related outcomes were recorded. Pregnancy loss, the need for repeat invasive testing, termination decisions, and delivery and neonatal outcomes were assessed.

Results: Major fetal structural anomalies were the leading indication (40%). Pathological genetic findings were identified in 21.4% of cases. Despite multimodal testing, 5.7% remained without a result, and 17.1% required repeat invasive sampling. No immediate complications occurred. Four pregnancy losses before 24 weeks' gestation (5.7%) were observed. Three occurred in pregnancies with major structural or chromosomal abnormalities, while one occurred in a structurally normal fetus with inconclusive cytogenetic results. When anomaly-associated cases were excluded, the observed loss rate among structurally normal pregnancies was 1.4%. No membrane rupture or chorioamnionitis occurred. Among live births, 97.2% were delivered at term. Neonatal outcomes were reassuring, and stillbirths (3.1%) were attributable to severe fetal or maternal pathology rather than the CVS procedure.

Conclusion: Structural fetal anomalies are now the leading indication for CVS. Post-procedure complications were rare, and most adverse outcomes were observed in pregnancies with underlying fetal or maternal pathology. These findings support the continued role of CVS as a diagnostic option in selected high-risk pregnancies.

Keywords: Chorionic villus sampling, prenatal diagnosis, genetic testing, chromosomal abnormalities, pregnancy outcomes, diagnostic yield, non-invasive prenatal testing, structural anomalies

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INTRODUCTION

Prenatal identification of genetic and chromosomal abnormalities has become a central component of contemporary obstetric and perinatal care. The detection of numerical and structural chromosomal anomalies, as well as of single-gene disorders, plays a critical role in risk assessment, counseling, and early pregnancy management.¹

Invasive diagnostic procedures such as chorionic villus sampling (CVS) and amniocentesis (AC) remain essential tools in this process and are supported by current professional guidelines, including those of the American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynaecologists, and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).²⁻⁴



CVS is typically performed between 10 and 14 weeks of gestation and enables retrieval of fetal genetic material several weeks earlier than AC, which is generally not recommended before 15 weeks because of an increased risk of complications.^{1,5} Achieving a diagnosis in the first trimester provides several important advantages, including reduced parental anxiety, earlier clinical decision-making, and the opportunity to perform pregnancy termination at a safer gestational age (GA) when indicated.^{1,6,7} Additional procedural benefits include the absence of direct fetal manipulation and of disruption to the fetal membranes. For these reasons, CVS has long been regarded as a reliable and effective first-trimester diagnostic option in experienced centers.⁸

Despite these strengths, several technical limitations may influence diagnostic accuracy. Maternal cell contamination (MCC), confined placental mosaicism, and culture failure can complicate the interpretation of CVS results and may necessitate further invasive testing in a subset of patients.^{9,10} Reported culture failure rates following CVS range from approximately 2.2% to 34%, while MCC rates range from 1.06% and 24.6%, reflecting substantial variability across centers and laboratory methodologies.

Although recent advances in prenatal screening, particularly non-invasive prenatal testing (NIPT), have reduced the number of invasive procedures, accurate counseling remains essential when offering CVS.^{11,12} Reported procedure-related pregnancy loss rates range from 0.7% to 3.2%.^{1,9,12,13} This variability may reflect differences in loss definitions, GA thresholds, and the inclusion of structurally or chromosomally abnormal pregnancies. Accordingly, counseling should incorporate accurate center-specific outcome data.¹²

The aim of this study was to evaluate the indications, diagnostic efficiency, procedural outcomes, and short-term pregnancy and neonatal outcomes of CVS performed in a tertiary referral center. By examining genetic testing methods, post-procedural complications, the need for repeat invasive testing, and subsequent pregnancy and neonatal outcomes, this study aims to provide contemporary outcome data from a high-risk referral population and to help inform clinical counseling and decision-making.

METHODS

This retrospective cohort included singleton pregnancies that underwent CVS between October 2023 and June 2025 at the Maternal–Fetal Medicine Unit of the University of Health Sciences Türkiye, İzmir City Hospital. The study protocol was approved by the University of Health Sciences Türkiye, İzmir City Hospital Ethics Committee (approval number: 2025/325, date: 09.07.2025).

Study Population and Indications

Pregnancies in which CVS was performed for genetic diagnosis were included in the study. Maternal age, gravidity, parity, number of living children, and GA at the time of the procedure were recorded. GA was determined by the last menstrual period or by first-trimester crown–rump length. Indications for CVS were categorized as follows: maternal anxiety, high-risk combined first-trimester screening test (cut-off >1/250), positive NIPT result, sonographic soft markers, major fetal structural anomalies, history of a previous child with aneuploidy or a genetic disease, parental carrier status for a chromosomal abnormality, and multiple indications (defined as the presence of more than one indication in the same patient).

Nuchal translucency (NT), included in the sonographic marker group, was measured by a maternal–fetal medicine specialist in accordance with the guidelines of the American Institute of Ultrasound in Medicine. Increased NT was defined as a measurement ≥ 3.0 mm during first-trimester sonography.¹⁴

All patients underwent a standardized first-trimester ultrasound examination in accordance with the ISUOG guidelines.¹⁵ All ultrasound examinations were performed using a Voluson E8 system (GE Healthcare, Wauwatosa, WI, USA) equipped with a 2–9 MHz convex transducer.

CVS Technique

All procedures were performed between 11 and 14 weeks of gestation. Prior to CVS, detailed counseling was provided about the results of screening tests, available invasive diagnostic options, and the benefits and limitations of each option. This was a retrospective study, and written informed consent was obtained from all patients.

Fetal viability, presentation, and placental location were evaluated before the procedure. CVS was performed under continuous ultrasound guidance using a double-needle technique, with the same ultrasound system and standardized protocol used for the first-trimester screening examinations. An 18-gauge needle was introduced transabdominally, without local anesthesia, to reach the placenta. After removal of the stylet, an assistant inserted a 20-gauge aspiration needle and manually aspirated placental villi. All procedures were carried out under aseptic conditions by a fellow physician under the direct supervision of a maternal–fetal medicine specialist. Immediately after the procedure, fetal heart activity, amniotic fluid volume, and the presence of any hemorrhage were assessed. Rh-negative and indirect Coombs-negative patients received 300 μ g of anti-D immunoglobulin for prophylaxis against alloimmunization.

Genetic Testing Protocol

All specimens were processed in the institutional genetics laboratory. Quantitative fluorescence polymerase chain reaction (QF-PCR) and conventional karyotyping were routinely performed.

Chromosomal microarray analysis (CMA) is not routinely performed in our clinic; instead, it is reserved for pregnancies with major fetal structural anomalies or increased NT, as well as for cases in which conventional karyotyping yields no result or yields a normal result despite high clinical suspicion. Next-generation sequencing (NGS) or Multiplex Ligation-dependent Probe Amplification (MLPA) was performed in a limited number of cases, including pregnancies with a relevant family history or suspicion of a single-gene disorder. The total number of patients evaluated with each genetic method was recorded.

Patients with abnormal results on any genetic test were assigned to the pathological group. Those in whom no results could be obtained from any genetic test were categorized as the no-result group. The number of pregnancy terminations within each indication group was also recorded.

Maternal, Pregnancy, and Neonatal Outcomes

Maternal, pregnancy, and neonatal outcomes included complications and pregnancy loss, such as vaginal bleeding, preterm premature rupture of membranes (PPROM), chorioamnionitis, and miscarriage. To provide more detailed information and to address potential discrepancies in definitions, we categorized all spontaneous losses into the following time intervals: 0–48 hours, 2–7 days, 7–14 days, and 2–24 weeks post-procedure. Patients who required repeat invasive testing, as well as those who accepted or declined repeat sampling, were recorded. Additional follow-up data included counseling on pregnancy termination; the number of terminations performed; maternal or fetal complications; hospital admissions and their indications; and stillbirths and live-birth outcomes. For subsequent pregnancies following CVS, follow-up data were collected from both hospital records and structured telephone interviews to investigate additional complications not documented in medical records. Birth characteristics, including preterm or term delivery, mode of delivery, and neonatal outcomes, were recorded for all live births. However, third-trimester follow-up data were unavailable for six patients. Therefore, variables related to late-pregnancy follow-up, hospital admissions, associated maternal–fetal conditions, and delivery and neonatal outcomes were evaluated in the remaining 64 patients.

Outcome Definitions

Primary outcomes were the diagnostic yield of CVS (proportion of pathological genetic findings across QF-PCR, karyotyping, CMA, NGS, and MLPA) and pregnancy loss rates (miscarriage, intrauterine death, stillbirth) from the procedure to neonatal follow-up.

Secondary outcomes included post-procedure complications (vaginal bleeding, PPRM, chorioamnionitis); need for repeat invasive testing; pregnancy termination rates; maternal/fetal complications [e.g., preeclampsia, fetal growth restriction (FGR)]; delivery characteristics (preterm birth, mode of delivery); and neonatal outcomes [birth weight, Apgar scores, neonatal intensive care unit (NICU) admission, neonatal loss].

In the present study, procedure-related pregnancy loss was not defined using a strict causal attribution model. Instead, pregnancy losses were categorized descriptively by the time interval following CVS and by the presence or absence of major fetal structural or chromosomal abnormalities.

Statistical Analysis

Descriptive statistical analyses were performed using the Statistical Package for the Social Sciences, version 26.0 (IBM Corp., Armonk, NY). Continuous variables were summarized as mean \pm standard deviation, and as ranges when appropriate, while categorical variables were reported as frequencies and percentages. Exact binomial 95% confidence intervals (CIs) were calculated for key proportions. Exploratory subgroup comparisons were performed using Fisher's exact test. Univariable logistic regression analysis was conducted to evaluate predictors of pathological genetic findings.

RESULTS

A total of 80 patients were initially scheduled for CVS between 2023 and 2025. The procedure could not be performed in 10 patients (12.5%): nine due to an unfavorable placental location (posterior; 11.3%) and one due to a pre-procedural missed miscarriage (1.3%), resulting in a final study cohort of 70 patients. A total of seven patients who were Rh-negative and indirect Coombs-negative received 300 μ g of anti-D immunoglobulin. The mean maternal age was 32.2 ± 5.8 years, and CVS was performed at a mean GA of 12.9 ± 0.8 weeks. Demographic characteristics of the study population are summarized in Table 1.

Table 2 presents the indications for CVS and associated diagnostic outcomes. Major fetal structural anomalies were the most frequent indication (40%, 28/70), among which there were 11 pathological results (39.3%) and 16 terminations (57.1%). An increased risk on the first-

trimester combined screening test accounted for 22.9% of cases; none of these cases yielded pathological genetic results. Maternal anxiety was the indication in 3 cases (4.3%), whereas an increased risk on NIPT (2.9%) resulted in abnormal findings in both patients. Sonographic soft markers represented 10% of indications, most commonly increased NT. One pathological result (14.3%) was identified in this group.

A prior pregnancy affected by a chromosomal abnormality was the indication for 6 patients (8.6%); none of these pregnancies showed a pathological finding, although one pregnancy was later terminated after micromelia suggestive of a skeletal dysplasia. Parental carrier status accounted for 2 cases (2.9%); one pathological result and one inconclusive result. Multiple indications were present in 6 patients (8.6%), including one patient with a pathogenic neurofibromatosis type 1 (NF1) variant. In another case, MCC was inconclusive, and the patient subsequently underwent AC, which identified a homozygous osteogenesis imperfecta-related variant,

leading to pregnancy termination. Exploratory subgroup comparisons of diagnostic yield across indication groups were performed using Fisher’s exact test. The rate of pathological findings was significantly higher in pregnancies with major fetal structural anomalies than in those with other indications (p<0.001). Univariable logistic regression analysis demonstrated that the presence of major fetal structural anomalies was significantly associated with pathological genetic findings (odds ratio 10.7%; 95% CI: 3.1–36.2; p<0.001). Overall, pathological genetic findings were identified in 15 of 70 cases (21.4%; 95% CI: 12.8–32.3). No diagnostic result was obtained in 4 of 70 cases (5.7%; 95% CI: 1.6–13.9), and pregnancy termination was performed in 20 of 70 cases (28.6%; 95% CI: 18.4–40.6).

Table 3 summarizes the genetic test results. QF-PCR identified 9 pathological findings (12.9%), including 45, X (monosomy X; Turner syndrome), trisomy 21 (n=3), trisomy 18 (n=3), and trisomy 13 (n=2), while 14 samples were non-informative. Conventional karyotyping detected 12 abnormalities (17.1%), including del(6)(p22), monosomy X, mosaic Turner syndrome, and multiple autosomal trisomies. Nineteen samples were inconclusive due to low band resolution, culture failure, MCC, or technical issues.

CMA was performed in 13 cases and identified three abnormalities (23.1%): a pathogenic 6p25.3–p24.1 microdeletion, trisomy 21, and monosomy X. The latter two had already been detected by karyotyping; thus, the 6p25.3–p24.1 microdeletion represented the additional diagnostic yield of CMA beyond conventional karyotyping (1/13 cases; 7.7%). NGS identified two likely pathogenic variants (NF1 and COL1A1), while one sample could not be analyzed due to MCC. MLPA confirmed one homozygous

Table 1. Demographic characteristics of the study population

n=70	Mean ± SD (min–max)
Age	32.2±5.8 (20–43)
Gravidity	2.3±1.4 (1–7)
Parity	0.94±0.98 (0–4)
Living children	0.90±0.97 (0–4)
Abortions	0.40±0.97 (0–5)
Gestational age (weeks)	12.9±0.8 (11–14)

SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Clinical indications for CVS and associated diagnostic outcomes

n=70	n (% of total)	Pathological result n (% within group)	No result n (% within group)	TOP n (% within group)
Maternal anxiety	3 (4.3)	-	1 (33.3)	-
Screen-positive test (1 st trimester)	16 (22.9)	-	-	-
Increased risk in NIPT	2 (2.9)	2 (100)	-	2 (100)
Sonographic markers	7 (10)	-	1 (14.3)	-
Increased NT	5 (7.1)	-	-	-
Others	2 (2.9)	-	1 (50)	-
Major fetal structural anomaly	28 (40)	11 (39.3)	1 (3.6)	16 (57.1)
Previous pregnancy with chromosomal abnormality	6 (8.6)	-	-	1 (16.7)
Parental chromosomal rearrangement carrier	2 (2.9)	1 (50)	1 (50)	1 (50)
Multiple indications	6 (8.6)	1 (16.7)	-	1 (16.7)
Total	70 (100)	15 (21.4)	4 (5.7)	20 (28.6)

TOP: Termination of pregnancy, NIPT: Non-invasive prenatal testing, NT: Nuchal translucency, CVS: Chorionic villus sampling

Table 3. Genetic test results				
Type of test n=70	n (% of total)	Pathological result n (%)	Normal result n (%)	No result n (%)
QF-PCR	70 (100)	9 (12.9) 1 45,X 3 T21 3 T18 2 T13	47 (67.1)	14 (20) ^a
KT	70 (100)	12 (17.1) 1 del(6)(p22) 1 45,X 1 47,XXX/45,X/46,XX (mosaic Turner syndrome) 3 T21 3 T18 3 T13	39 (55.7)	19 (27.1) ^b
CMA	13 (18.6)	3 (23.1) 1 6p25.3–p24.1 del (pathogenic) 1 T21 1 45,X	8 (61.5)	2 (15.4) ^c
NGS	4 (5.7)	2 (50) 1 NF1 c.1466A>G (p.Tyr489Cys) 1 COL1A1 p.Gly626Asp (heterozygous, likely pathogenic)	1 (25)	1 (25)
MLPA	1 (1.4)	1 (100) SMN1 exons 7–8 (homozygous deletion)		

^aIn 8 cases, no result was obtained due to maternal cell contamination. It was recommended to wait for the cytogenetic results for 2 patients with chromosome 13 anomaly, 1 patient with chromosome 18 anomaly, and 2 patients with sex chromosomes

^bNo result due to low band resolution (n=3), maternal cell contamination (n=3), culture failure (n=7), or technical issues (n=6)

^cNo result due to maternal cell contamination (n=1) or technical issues (n=2)

Maternal cell contamination was observed in 20 cases overall and contributed to inconclusive results in QF-PCR (n=4), karyotyping (n=2), QF-PCR + karyotyping (n=2), and QF-PCR + CMA (n=2). For each test modality, percentages in the "Pathological," "Normal," and "No result" columns reflect within-group distributions, calculated relative to the number of patients who underwent that specific test ("n tested").

QF-PCR: Quantitative fluorescence polymerase chain reaction, CMA: Chromosomal microarray analysis, KT: Conventional karyotype analysis, NGS: Next-generation sequencing, MLPA: Multiplex ligation-dependent probe amplification, T: Trisomy

Note: For each test modality, percentages in the "pathological," "normal," and "no result" columns reflect within-group distributions, calculated relative to the number of patients who underwent that specific test ("n tested")

SMN1 deletion. Overall, pathological findings in the cohort included trisomy 21 (4.3%), trisomy 18 (4.3%), trisomy 13 (4.3%), monosomy X (1.4%), mosaic Turner syndrome (1.4%), a pathogenic 6p deletion (1.4%), an NF1 variant (1.4%), a homozygous SMN1 deletion (1.4%), and a likely pathogenic COL1A1 variant (1.4%).

A total of 70 CVS procedures were evaluated for short- and intermediate-term outcomes (Table 4). No immediate complications occurred within the first 48 hours. Two patients experienced early pregnancy loss within the first two weeks (2.8%; 95% CI: 0.3–9.7). Repeat invasive testing was required in 12 patients (17.1%) because initial results were inconclusive or incomplete, most commonly secondary to MCC, culture failure, or other technical limitations.

Termination of pregnancy was recommended in 23 cases (32.9%) and performed in 20 cases (28.6%). The mean GA at termination was 15.4±3.3 weeks (range: 11–22). Additional

maternal–fetal complications occurred in two pregnancies (3.1%): one pregnancy developed preeclampsia with placental abruption, and the other involved a fetus with trisomy 21 that demonstrated early-onset FGR. Hospitalization was required in three cases (4.7%): one case due to FGR related to trisomy 21 and two cases due to complications associated with diabetes.

Stillbirth occurred in two pregnancies (3.1%): one associated with multiple fetal anomalies and the other in the setting of severe preeclampsia with placental abruption. Among the 64 pregnancies with available delivery outcomes, 36 resulted in live births, in line with expectations for a clinically high-risk CVS population.

Pregnancy loss between 2–24 weeks occurred in two additional cases (2.9%), both were associated with major fetal anomalies: megacystis with trisomy 13 and cystic hygroma with trisomy 18. The detailed clinical characteristics of all pregnancy loss cases are summarized in Table 5.

	Mean ± SD or n (%)	Description/notes
Early and intermediate outcomes (n=70)		
Complication/loss (0–2 days)	0 (0)	
Complication/loss (2–7 days)	1 (1.4)	
Complication/loss (7–14 days)	1 (1.4)	
Complication/loss (2–24 weeks)	2 (2.8)	
Repeat invasive procedure required	12 (17.1)	5/12 (41.7%) accepted repeat testing*
Termination recommended	23 (32.9)	
Termination performed	20 (28.6)	
Gestational age at termination (weeks)	15.4±3.3 (range 11–22)	
Late pregnancy and delivery outcomes (n=64)		
Maternal/fetal complications	2 (3.1)	1 severe preeclampsia with placental abruption 1 early-onset FGR associated with T21
Hospitalization required	3 (4.7)	1 early-onset FGR associated with T21 2 preterm labor
Stillbirth	2 (3.1)	1 multiple anomalies 1 preeclampsia with abruption
Live birth	36 (56.3)	

*Structural evaluation was inconclusive due to maternal cell contamination (n=2), low band resolution (n=3), culture failure (n=6), or need for additional genetic investigations (n=1)
FGR: Fetal growth restriction, SD: Standard deviation, CVS: Chorionic villus sampling, T: Trisomy

Case	Maternal age	GA at CVS (weeks)	GA at pregnancy loss (weeks)	Structural anomaly	Genetic result	MCC	Culture failure	Clinical context
1	42	13	14	-	QF-PCR normal; culture failure	-	1	Screen positive test results
2	35	12	14	Megacystis, increased NT	T13	-	-	Megacystis, increased NT
3	31	13	13	Megacystis	Normal	1	-	Megacystis
4	31	11	14	Cystic hygroma	Normal	-	-	Cystic hygroma

GA: Gestational age, CVS: Chorionic villus sampling, MCC: Maternal cell contamination, QF-PCR: Quantitative fluorescence polymerase chain reaction, NT: Nuchal translucency

Overall, pregnancy loss occurred in 4 of 70 pregnancies (5.7%). Three losses were associated with major fetal structural or chromosomal abnormalities, whereas one occurred in a structurally normal fetus with inconclusive cytogenetic results. When pregnancies with major anomalies were excluded, the observed loss rate among structurally normal pregnancies was 1.4% (1/70).

Delivery outcomes among the 36 live births are summarized in Table 6. Of these, 35 (97.2%) delivered at term, while one patient (2.8%) delivered preterm at 35 weeks due to trisomy 21. Spontaneous vaginal delivery

occurred in 25% of cases, and primary cesarean section occurred in 30.6% of cases. One neonatal death (2.8%) occurred due to cardiac failure related to trisomy 21. The mean GA at delivery was 38.2±1.1 weeks, and the mean birth weight was 3131±570 g. NICU admission was required for 13.9% of neonates; sex distribution was balanced (52.8% female and 47.2% male).

DISCUSSION

This study provides a detailed evaluation of CVS indications, diagnostic yield, and associated pregnancy and neonatal outcomes in this cohort. The results

Table 6. Delivery and neonatal outcomes	
n=36	Mean ± SD or n (%)
Term delivery	35 (97.2)
Preterm delivery (<37 weeks)	1 (2.8)*
Spontaneous vaginal delivery	9 (25)
Primary cesarean section	11 (30.6)
Repeat cesarean section	16 (44.4)
Neonatal loss	1 (2.8)**
Gestational age at birth (weeks)	38.2±1.1 (range 35–41)
Birth weight (g)	3131.3±570.1
Female newborns	19 (52.8)
Male newborns	17 (47.2)
Apgar score (1 min)	7.89±1.01
Apgar score (5 min)	9.03±0.97
NICU admission	5 (13.9)
*35 weeks, T21	
**Neonatal death secondary to cardiac failure, T21	
g: Grams, min: Minute, NICU: Neonatal intensive care unit, SD: Standard deviation, T: Trisomy	

demonstrate that major fetal structural anomalies represent the leading indication for CVS and are associated with the highest rate of pathological genetic findings. This association was further supported by exploratory statistical analyses, including Fisher's exact test and univariable logistic regression, which showed a significantly higher likelihood of pathological findings in pregnancies with structural anomalies. In contrast, post-procedure pregnancy loss rates were low in this cohort and occurred predominantly in pregnancies with significant underlying fetal or maternal risk factors.

Pathological genetic results were identified in 21.4% of cases. Although trisomy 21 is typically the most commonly reported aneuploidy, trisomy 18 occurred at a similar frequency in our cohort.^{7,9,16} This pattern likely reflects the high prevalence of structural anomalies in our population (40%), which exceeds rates reported in most studies, in which an increased risk on first-trimester screening tests is usually the most common indication.^{1,9,12} This may be related to the profile of a tertiary referral center with advanced ultrasound technology and experienced fetal imaging specialists. Moreover, the widespread adoption of NIPT in recent years has not only begun to replace traditional first-trimester screening but has also led to a reduction in invasive diagnostic procedures among women identified as high-risk by first-trimester screening.^{17,18} This shift may also explain why elevated first-trimester screening risk is no longer the most common indication for CVS in our cohort. Current guidelines

indicate that NIPT is a screening test requiring confirmation by invasive procedures such as CVS or AC.¹⁹ Nevertheless, rare autosomal trisomies are frequently associated with fetal or confined placental mosaicism, which may result in discordance between placental and fetal genetic findings; therefore, AC may be preferred to confirm true fetal involvement when mosaicism is suspected.^{20,21}

Changes in clinical practice have also affected the role of advanced maternal age (AMA). Current guidelines from ACOG no longer recommend AMA as a stand-alone indication for invasive testing.²² Nevertheless, many published series still report that CVS procedures were performed solely for AMA.^{1,9,23} In our cohort, no patients underwent CVS solely for AMA. Relatively few studies appear to reflect this recent shift in clinical practice.¹² Spinal muscular atrophy (SMA) carrier screening is now widely recommended.^{24,25} Several studies have supported the use of CVS for prenatal diagnosis in pregnancies at risk for SMA.²⁶⁻²⁹

Although our sample size was limited, our findings highlight the relevance of CVS for SMA carrier couples. As carrier screening programs expand, prenatally diagnosed SMA cases are expected to increase, further strengthening the evidence base for this indication.

Reported pregnancy loss rates after CVS vary across studies, largely due to differences in study design and definitions of procedure-related pregnancy loss.^{1,9,11-13} Previous studies have reported higher pregnancy loss rates in women aged ≥40 years, both following CVS and in the general obstetric population.³⁰ In addition, several studies have evaluated both the expected miscarriage risk based on maternal and fetal characteristics and the observed miscarriage rates following CVS.^{12,31} In these analyses, no significant increase in miscarriage risk attributable to the procedure was observed. In our study, pregnancy losses were reported according to commonly used time-based categories. No immediate complications, such as vaginal bleeding or PPROM, were observed; however, four pregnancy losses occurred before 20 weeks. Three were associated with major structural or chromosomal abnormalities, while one occurred in a pregnancy without identifiable structural or chromosomal abnormalities. When anomaly-associated cases were excluded, the observed loss rate among structurally normal pregnancies was 1.4%. Pregnancy losses observed following CVS appeared to be predominantly attributable to underlying fetal pathology or AMA. Post-procedure loss rates remained low in this cohort. However, establishing any causal link to the procedure is difficult because of the retrospective design, small sample size, low number of events, and confounding by indication in this high-risk population.

CVS remains an important option when confirmatory testing is required for pregnancy termination decisions, despite advances in NIPT.³² Published termination rates following CVS range from 16% to 29%, and our findings fall within the upper range of previously reported rates.^{1,9,12} This finding likely reflects early and accurate prognostic assessment enabled by detailed ultrasound evaluation and contemporary genetic testing strategies.

Non-informative results can occur due to confined placental mosaicism, insufficient villus sampling, or limited cytogenetic resolution.^{1,10} When considered individually, culture failures were observed in 27.1% of cases; however, only 5.7% of patients remained without a definitive diagnosis after applying additional genetic testing methods. These findings are consistent with the potential benefit of multimodal testing strategies. Nonetheless, 17.1% of patients required repeat invasive testing, and more than half declined a second procedure, highlighting the need to consider AC early, particularly when mosaicism is suspected.⁹ MCC was an important cause of inconclusive genetic results in our cohort. Although MCC is a recognized limitation of CVS, the occurrence of MCC may also reflect sampling technique, placental characteristics, or laboratory processing factors. Therefore, reducing MCC rates through optimized sampling strategies and laboratory protocols may improve diagnostic efficiency and decrease the need for repeat invasive procedures. However, the determinants of CVS sampling failure remain incompletely understood.¹⁰ Chevreau et al.¹⁰ reported a 34% failure rate, independent of operator experience, and emphasized the need for careful pre-procedural assessment to reduce unsuccessful sampling and repeat procedures.

Regarding obstetric complications, Movahedi et al.³³ reported that PPRM and FGR were the most frequent observed complications following CVS, while no cases of chorioamnionitis were identified. In our cohort, no cases of PPRM were observed, and FGR occurred in only one pregnancy affected by trisomy 21. Similarly, other studies have reported chorioamnionitis as a rare complication following CVS.^{33,34}

In our cohort, preeclampsia occurred in only one of 44 ongoing pregnancies that had third-trimester follow-up. This case was complicated by placental abruption and stillbirth. Although the overall prevalence was comparable to that reported in the general population (4.6%),³⁵ the severity of this case highlights the importance of close monitoring.

Neonatal outcomes following CVS have been evaluated in a limited number of studies.³⁶ In that large retrospective cohort, the mean GA at delivery was 38.4 weeks, with a preterm birth rate of 10.5%. Cesarean delivery occurred in

53.0% of cases; the mean birth weight was approximately 3158 g, and NICU admission was required in 13.0% of neonates; there was no significant increase in composite neonatal morbidity compared with AC. Our study provides a comprehensive evaluation of indications, genetic findings, and perinatal, obstetric, and neonatal outcomes within a single cohort. Despite the high-risk characteristics of the population, delivery outcomes were generally favorable. Most pregnancies reached term (mean GA of 38.2 weeks); preterm delivery occurred in only one case (2.8%; trisomy 21), and neonatal loss was limited to a single case of trisomy 21. Stillbirth (3.1%) was attributable to severe fetal or maternal pathology rather than to the CVS procedure. The high prevalence of previous cesarean deliveries reflected the underlying obstetric risk profile. Overall, obstetric and neonatal outcomes in this tertiary referral cohort were generally favorable, although these observations are tempered by the study's limitations.

The present study has several limitations. First, the relatively small sample size and the limited number of events reduce the statistical power of the analyses and preclude more extensive multivariable modeling. Second, the retrospective single-center design introduces the potential for referral bias, because our institution is a tertiary referral center that frequently receives high-risk pregnancies with suspected fetal anomalies. Third, confounding by indication cannot be excluded, since pregnancies undergoing CVS often have underlying clinical risk factors that may independently influence pregnancy outcomes. Fourth, no predefined adjudication criteria were applied to attribute pregnancy loss specifically to the CVS procedure rather than to underlying fetal or maternal pathology; therefore, causal attribution should be interpreted with caution. Although all procedures were performed by fellows under the supervision of maternal-fetal medicine specialists, operator experience may influence procedural success, MCC, and complication rates, and should therefore be considered when interpreting the results. Finally, long-term neonatal or neurodevelopmental follow-up data were not available, limiting the ability to assess potential late outcomes beyond the perinatal period.

CONCLUSION

These findings suggest that the indications for CVS are increasingly shifting toward pregnancies with structural fetal anomalies. Our findings indicate that CVS continues to play an important role in definitive prenatal diagnosis, accurate counseling, and timely pregnancy management and that observed post-procedure complication rates were low in both the prenatal and neonatal periods. Post-procedure pregnancy losses in this cohort predominantly occurred in pregnancies with significant fetal or maternal

risk factors and were less frequently observed in structurally normal cases. The results also emphasize the importance of informing families that, in selected cases, additional invasive testing may be required. However, given the retrospective design and single-center nature of the study, these observations should be interpreted cautiously and confirmed in larger, multicenter prospective studies to enhance generalizability and strengthen the evidence base for clinical practice.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, İzmir City Hospital Ethics Committee (approval number: 2025/325, date: 09.07.2025).

Informed Consent: This was a retrospective study, and written informed consent was obtained from all patients.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.E.Ç., H.G., B.B., İ.G.A., H.A.A., E.B., S.K., A.K., A.E., Concept: Z.E.Ç., H.G., A.E., Design: Z.E.Ç., H.G., Data Collection or Processing: S.H.Ö., R.T., İ.G.A., H.A.A., E.B., Analysis or Interpretation: Z.E.Ç., S.H.Ö., Literature Search: Z.E.Ç., H.G., Writing: Z.E.Ç., H.G., A.E.

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Suprapatellar Entry Intramedullary Nailing in Adult Tibial Shaft Fractures: A Retrospective Clinical Study

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ABSTRACT

Objective: The tibia is one of the most commonly fractured long bones and is frequently exposed to high-energy trauma. Selecting an appropriate treatment method is essential for successful outcomes and improved patient quality of life. In recent years, the suprapatellar entry intramedullary nailing technique has gained attention as a promising surgical approach. The aim of this study was to evaluate the clinical and radiological outcomes of suprapatellar intramedullary nailing in the treatment of adult tibial shaft fractures.

Methods: This retrospective study included adult patients with tibial shaft fractures treated with the suprapatellar intramedullary nailing technique. Fractures were classified using the Arbeitsgemeinschaft für Osteosynthesefragen classification system. Both open and closed fractures were included, and open fractures were classified according to the Gustilo–Anderson classification. Clinical and radiological outcomes were evaluated during follow-up.

Results: The mean postoperative fracture healing time was approximately 9 months. Most patients reported minimal anterior knee pain, with only occasional cases of limited knee motion. Observed complications included superficial infections, minor angular deformities, and small limb length discrepancies. Dynamization was required in two patients. The average operative time was approximately 52 minutes.

Conclusion: Suprapatellar intramedullary nailing represents a reliable and effective surgical option for the treatment of adult tibial shaft fractures. The technique may facilitate fracture reduction and result in favorable clinical outcomes with acceptable complication rates.

Keywords: Tibial shaft fracture, intramedullary nailing, suprapatellar entry

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INTRODUCTION

Tibial shaft fractures are among the most common long bone fractures in the adult population and are predominantly the result of high-energy trauma.¹ The primary goals in the treatment of these fractures are to achieve stable union while preserving limb length, alignment, and rotation, and to restore the patient's functional capacity as early as possible.² Accurate classification is essential for treatment planning, and the AO classification system remains the most widely used method in clinical practice (Figure 1).³

Traditionally, tibial intramedullary nailing has been performed through an infrapatellar entry portal with

the knee in a flexed position. However, the infrapatellar approach has been reported to complicate fracture reduction, particularly in proximal and distal tibial shaft fractures, and to increase the risk of malalignment.^{4,5} In addition, this approach has been associated with the development of postoperative anterior knee pain.⁵ For these reasons, the suprapatellar entry technique performed with the knee in a semi-extended position has gained increasing attention in recent years.^{4,6}

The suprapatellar approach has been reported to offer several surgical advantages, including easier fracture reduction, improved fluoroscopic visualization, and better



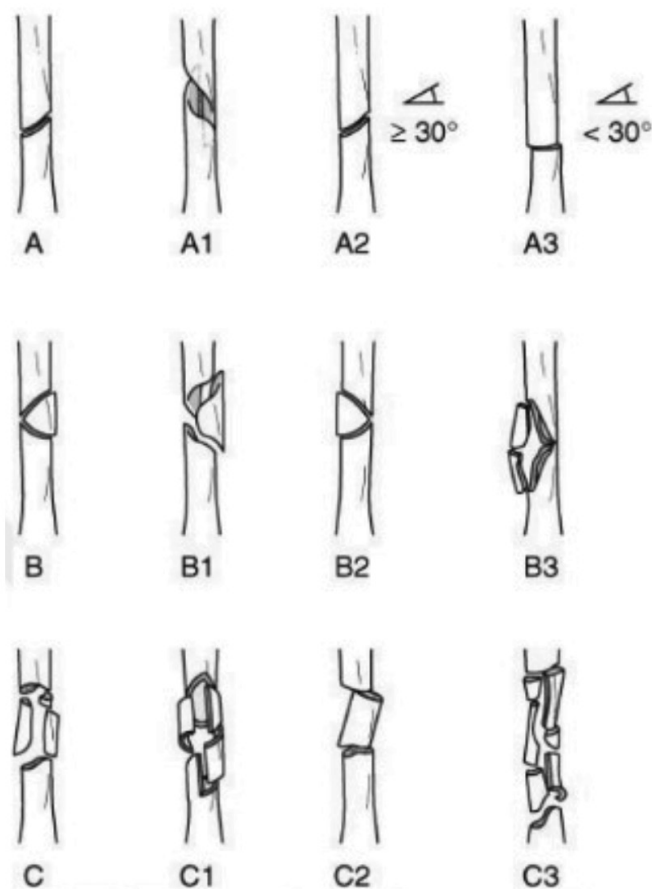


Figure 1. AO classification of tibial fractures

AO: *Arbeitsgemeinschaft für Osteosynthesefragen*

control of the mechanical axis.^{6,7} Clinical studies have demonstrated that suprapatellar nailing may reduce the rate of malalignment compared with the infrapatellar technique while providing at least equivalent functional outcomes.^{8,9} Furthermore, recent systematic reviews and meta-analyses support the suprapatellar approach as a safe and effective alternative, particularly for proximal and distal tibial shaft fractures, demonstrating lower malalignment rates and comparable clinical outcomes.^{9,10}

The aim of this study is to evaluate the clinical and radiological outcomes of suprapatellar-entry locked intramedullary nailing for the treatment of adult tibial shaft fractures and to discuss the findings in the context of the current literature. Particular emphasis was placed on coronal and sagittal alignment parameters, functional outcomes, and the incidence of anterior knee pain, which remain critical concerns in intramedullary nailing and are frequently addressed in comparison with the traditional infrapatellar approach.

METHODS

Study Design and Patient Selection

This retrospective observational study was conducted at a single tertiary referral center. A total of 25 adult patients with tibial shaft fractures who underwent suprapatellar intramedullary were included in the study. Patients younger than 18 years, those with fractures exhibiting intra-articular extension, those with type III open fractures, or those with pseudoarthrosis following surgery were excluded from the study. All eligible patients were invited for follow-up evaluation, and the 25 patients who attended the final assessment constituted the study cohort. Among the patients, 7 were female and 18 were male. The mean age was 45 years (range: 18–68) among female patients and 40.1 years (range: 20–75) among male patients. Two fractures were open, and 23 were closed. According to the Gustilo–Anderson classification, one open fracture was type I and another was type II. Fractures were classified according to the AO classification system as type A in 14 patients (56%), type B in 6 patients (24%), and type C in 5 patients (20%). Based on fracture location, 7 fractures (28%) were proximal, 10 (40%) were mid-shaft, and 8 (32%) were distal. Radiological evaluation included assessment of coronal and sagittal alignment on standard anteroposterior and lateral radiographs. Malalignment was defined as an angular deformity of $\geq 5^\circ$ in any plane. Rotational alignment was assessed clinically and radiographically by comparing limb positioning and cortical continuity. Leg length discrepancy was measured using orthoradiographic imaging, and shortening of ≥ 1 cm was recorded. All radiographic evaluations were performed at final follow-up. With regard to associated injuries, one patient had a rib fracture, another had a distal radius fracture, and a third had a proximal humerus fracture. The remaining patients had isolated tibial fractures. The patient with a rib fracture did not have a pulmonary contusion; therefore, reamed intramedullary nailing was not contraindicated. All patients underwent surgery within the first week following injury.

The study protocol was approved by the Sakarya University Ethics Committee (approval number: 71522473/050.01.04/35, date: 28.02.2017).

Radiological Evaluation

Radiological assessment was performed using standardized anteroposterior and lateral radiographs at the final follow-up. Coronal and sagittal alignment was evaluated by measuring the angulation between proximal and distal fracture fragments.

Malalignment was defined as an angular deformity of $\geq 5^\circ$ in either the coronal or sagittal plane. Rotational alignment

was assessed clinically by comparing the foot progression angle and limb symmetry, and radiographically by evaluating cortical continuity.

Leg length discrepancy was measured using orthoradiographic imaging, and shortening of ≥ 1 cm was considered clinically relevant.

Surgical Procedure

All procedures were performed under general, spinal, or epidural anesthesia without the application of a tourniquet. With the knee in approximately 10–15° of flexion (semi-extended position), a longitudinal incision approximately 3 cm in length was made proximal to the patella (Figure 2). Access to the patellofemoral joint was achieved through the quadriceps tendon, and a cannula was introduced into the anterior cortex of the proximal tibia under fluoroscopic guidance. A guidewire was advanced across the fracture site to the distal tibia under fluoroscopic control (Figure 3). After appropriate positioning was confirmed, sequential reaming of the medullary canal was performed, and a preselected locked intramedullary nail was inserted. Reduction and alignment were assessed fluoroscopically. Distal locking screws were placed using the free-hand technique, followed by placement of proximal locking screws. All fractures were treated with closed reduction and statically- or dynamically- locked nails as indicated.

Postoperative Management and Follow-up

Postoperatively, no splinting was applied. Weight-bearing was gradually increased based on fracture characteristics and patient tolerance. Full weight-bearing without support was allowed after radiological evidence of union. The mean postoperative hospital stay was 4 days

(range: 2–8 days). Patients were followed monthly with clinical and radiographic evaluations.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows software. Continuous variables were expressed as mean \pm standard deviation, and categorical variables as number and percentage. The normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons between male and female patients regarding fracture healing time, follow-up duration, Lysholm score, and Cincinnati score were performed using the independent samples t-test. A p value < 0.05 was considered statistically significant. Parametric tests were applied because the continuous variables were normally distributed according to the Shapiro–Wilk test.

RESULTS

The clinical and radiological outcomes of the 25 patients who attended the final follow-up evaluation were analyzed. The average follow-up duration of our patients was 14.8 months (range: 6 to 24 months). The average fracture union time was 9.14 months (range: 6 to 15 months) (Table 1).

The patients were evaluated according to the Lysholm and Cincinnati functional scoring systems. The average Lysholm score was 90.8 (range: 64–100), and the average Cincinnati score was 26 (range: 15–30). Four patients experienced minimal patellofemoral pain, while the remaining patients experienced none. The patients were also assessed for joint range of motion limitations. Four patients had 110 degrees of knee flexion. Based on these results, all patients reported being satisfied with the surgery (Table 2).

Table 1. Some descriptive data of the patients

	Min	Max	Mean \pm SD
Age (year)	18	75	42.6 \pm 16.33
Healing time (month)	6	15	9.14 \pm 2.98
Follow-up period (Month)	6	24	14.83 \pm 5.30
Lysholm	64	100	90.88 \pm 9.30
Cincinnati	15	30	26.83 \pm 3.81

SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. Comparison of healing time, follow-up duration, Lysholm, and Cincinnati scores according to gender

	Male	Female	p value
Healing time (month)	9.19 \pm 3.29	9 \pm 2	0.90
Follow-up period (Month)	15.18 \pm 4.29	14 \pm 7.59	0.63
Lysholm	91.06 \pm 10.59	90.43 \pm 5.68	0.88
Cincinnati	27.71 \pm 3.01	24.7 \pm 5.09	0.08



Figure 2. (a) Marking of the incision site. (b) Making the suprapatellar incision. (c) Surgical painting and draping procedures

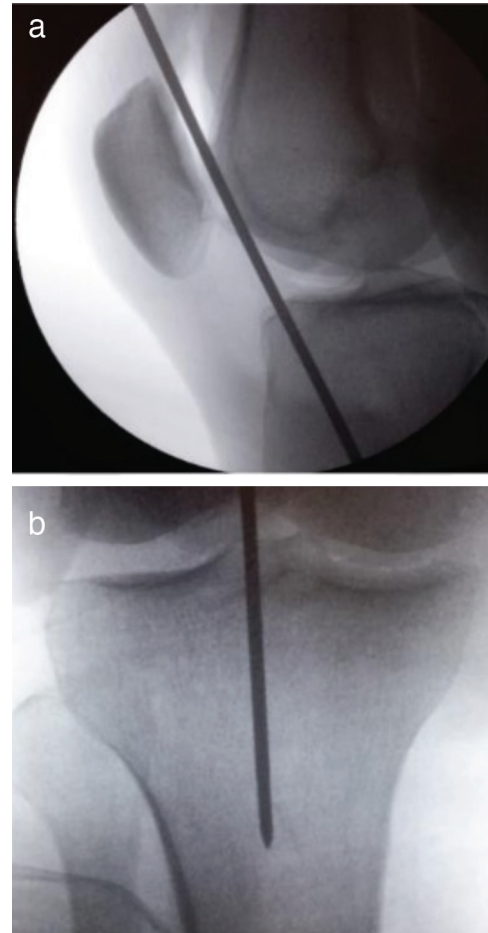


Figure 3. (a) The lateral fluoroscopic image of the guidewire sent as suprapatellar. (b) The anterior posterior fluoroscopic image of the guidewire sent as suprapatellar

Two patients reported discomfort only while sitting with their knees flexed. None of these patients developed compartment syndrome. In 1 patient (4%), a valgus deformity with an angulation between 5° and 10° was observed. Anterior displacement of the distal fragment of over 5° occurred in only 1 patient (4%); however, the patient had no clinical complaints. Only 1 patient (4%) had a 1 cm leg-length discrepancy, which was detected incidentally on an orthoradiogram. The patient had no clinical complaints. The functional outcome scores of patients with radiological malalignment or leg-length discrepancy were analyzed individually. These patients had Lysholm and Cincinnati scores within the overall cohort range and did not exhibit a statistically significant deterioration in functional outcome. The minor radiological deviations detected did not translate into clinically relevant functional limitations at the final follow-up. Superficial infections developed in only 2 cases (8%). These were open fractures, and the infections resolved with antibiotic therapy.

DISCUSSION

The principal finding of this study is that suprapatellar intramedullary nailing provided satisfactory coronal and sagittal alignment, favorable functional outcomes, and a low incidence of anterior knee pain in adult tibial shaft fractures.

Comparisons of suprapatellar and infrapatellar approaches for tibial intramedullary nailing have demonstrated broadly similar clinical outcomes, with differences primarily in alignment control and knee-related symptoms.¹⁰ Meta-analytical data further suggest that the suprapatellar approach may facilitate maintenance of fracture reduction, particularly in fractures with a tendency toward malalignment.¹¹ In our study, satisfactory radiological alignment was achieved in the majority of patients, supporting the effectiveness of the suprapatellar technique in maintaining fracture reduction.

Functional outcomes following tibial shaft fracture fixation have been extensively evaluated in the literature. Systematic reviews have shown no significant differences in patient-reported outcome measures between suprapatellar and infrapatellar approaches.^{12,13} Consistent with these findings, patients in our series achieved acceptable functional recovery without clinically relevant limitations in activities of daily living.

Anterior knee pain remains one of the most commonly reported complaints after tibial intramedullary nailing. Several comparative studies have suggested that suprapatellar entry may be associated with a lower incidence of anterior knee pain than infrapatellar entry.¹⁴ Clinical investigations have also indicated that preservation of the extensor mechanism and avoidance of patellar tendon violation may reduce postoperative knee discomfort.¹⁵ In our cohort, anterior knee pain was infrequent and mild, which further supports the potential benefit of the suprapatellar entry technique.

Rotational alignment is a critical determinant of long-term functional outcome after tibial shaft fracture fixation. Recent studies have demonstrated a lower prevalence of rotational malalignment with suprapatellar nailing compared with infrapatellar techniques.¹⁶ Improved limb control and fluoroscopic visualization in the semi-extended position are thought to contribute to this advantage. In our study, no clinically significant rotational deformity was detected, consistent with these observations.

Concerns regarding the risk of knee sepsis associated with intra-articular instrumentation during suprapatellar nailing have been addressed in several clinical studies. Available evidence indicates that suprapatellar nailing is not associated with an increased incidence of postoperative

knee sepsis, even in open tibial fractures.^{17,18} In our study, no cases of septic arthritis occurred; superficial infections were limited in number and resolved with appropriate treatment.

Recent systematic reviews comparing suprapatellar, parapatellar, and infrapatellar techniques have concluded that suprapatellar nailing is a safe and effective option with acceptable complication rates and reliable alignment control.^{19,20} Furthermore, contemporary reviews and technical descriptions have emphasized that refinements in surgical technique and instrumentation have enhanced the safety and reproducibility of the suprapatellar approach.²¹ In our experience, the use of modern suprapatellar instrumentation facilitated accurate nail insertion and stable fixation, which likely contributed to the favorable clinical and radiological outcomes.

This study has several methodological limitations that should be acknowledged. First, the retrospective design may introduce potential selection bias and limit the ability to establish causal relationships. Second, the relatively small sample size may reduce statistical power and restrict the generalizability of the findings. Third, the absence of a comparative control group precludes direct comparison of the suprapatellar approach with alternative techniques, particularly the infrapatellar approach.

CONCLUSION

Suprapatellar entry intramedullary nailing provided satisfactory coronal and sagittal alignment, favorable functional outcomes, and a low incidence of anterior knee pain in adult tibial shaft fractures. The semi-extended position may facilitate fracture reduction and improve intraoperative alignment control. Radiological deviations observed in this series were minimal and did not result in clinically significant functional impairment. Complication rates were acceptable, and no major implant-related or intraarticular infectious complications were observed.

Although the retrospective design and limited sample size restrict the strength of definitive conclusions, the findings of this study suggest that the suprapatellar approach is a reliable and effective surgical option for appropriately selected adult tibial shaft fractures.

Ethics

Ethics Committee Approval: The study protocol was approved by the Sakarya University Ethics Committee (approval number: 71522473/050.01.04/35, date: 28.02.2017).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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Evaluation of Triglyceride Glucose Index and Systemic Inflammatory Biomarkers in Non-Diabetic Patients with Adhesive Capsulitis: A Cross-Sectional Clinical Study

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ABSTRACT

Objective: Adhesive capsulitis (AC) is a painful shoulder condition characterized by progressive restriction of active and passive range of motion. This study aimed to compare the triglyceride–glucose (TyG) index and haematology-derived inflammatory indices between patients with AC and healthy controls and to evaluate their associations with the presence of AC.

Methods: In this study, the demographic data, clinical findings and laboratory results of non-diabetic patients with AC were evaluated. Fasting plasma glucose (FPG), lipid profile [triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol], C-reactive protein (CRP), vitamins D and B12, and complete blood count, obtained within the preceding 3 months, were recorded. The TyG index, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) were calculated.

Results: Seventy-one participants were included (38 controls and 33 AC). The AC group was older and had higher body mass index (both $p \leq 0.001$). FPG ($p = 0.010$), LDL ($p = 0.001$), total cholesterol ($p = 0.049$), and TyG index ($p = 0.020$) were higher in AC, whereas NLR, PLR, SII, CRP, HDL, vitamin D, and B12 were comparable between groups (all $p > 0.05$). In adjusted models, age was a consistent predictor of AC [adjusted odds ratio (aOR) 1.094, 95% confidence interval (CI) 1.036–1.155; $p = 0.001$], and LDL was independently associated with AC (aOR 1.019, 95% CI 1.001–1.037; $p = 0.044$).

Conclusion: Non-diabetic AC was associated with metabolic dysregulation, while haematology-derived inflammatory indices remained comparable to controls. Beyond symptomatic management, clinicians should consider screening patients with AC for metabolic dysregulation, as this may aid risk stratification and care.

Keywords: Adhesive capsulitis, blood glucose level, blood triglycerides level, inflammation

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INTRODUCTION

Adhesive capsulitis (AC) is a painful shoulder disorder characterised by restricted movement.¹ It affects approximately 2–5% of the general population and occurs more frequently among individuals with metabolic and endocrine comorbidities.² While AC has traditionally been viewed as a local mechanical and inflammatory disorder, growing evidence suggests that chronic low-grade inflammation and metabolic dysfunction may also contribute to its pathogenesis.³ The risk of AC is particularly

increased in individuals with diabetes mellitus (DM).⁴ More broadly, metabolic and endocrine abnormalities have been linked to AC; inflammatory and other metabolic profiles may influence disease development and clinical course.⁵

Studies evaluating glucose-related parameters in AC have yielded inconsistent findings, with some reporting associations with symptom severity and others showing no differences in blood glucose compared with controls.^{6–10} In contrast, adverse lipid profiles—particularly higher total cholesterol and triglyceride levels—have been associated



with AC.^{11,12} Thyroid dysfunction may also contribute to pro-inflammatory and fibrotic pathways relevant to AC.¹³ Overall, these observations support further investigation of immunometabolic markers in AC.

The triglyceride–glucose (TyG) index is a practical surrogate marker of insulin resistance, calculated from fasting triglyceride and glucose values, and is readily available in clinical practice.^{14,15} It has also been used as an indicator of metabolic syndrome.¹⁶ Haematology-derived inflammatory indices, obtained from routine complete blood count parameters, are increasingly used as accessible markers of systemic inflammation. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are widely used indices,¹⁷ and the systemic immune-inflammation index (SII), combining neutrophil, lymphocyte and platelet parameters, has also been proposed as a useful marker of systemic inflammation.¹⁸

It is increasingly emphasised that AC may involve systemic inflammation and metabolic disturbances beyond localised pathology.^{2,3} Given that insulin resistance has been linked to increased pain and restricted movement in AC,² further studies focusing on the immunometabolic profile are warranted. Accordingly, we compared the TyG index and haematology-based inflammatory indices between non-diabetic patients with AC and age- and sex-matched healthy controls and evaluated their associations with the presence of AC. We hypothesised that non-diabetic patients with AC would have a higher TyG index and a more pro-inflammatory haematological profile than controls, and that higher TyG index and inflammatory markers would be independently associated with AC.

METHODS

This was an observational, cross-sectional, case-control study involving prospective recruitment. It compared non-diabetic patients with AC to age- and sex-matched healthy controls. Approval was obtained from the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu Ethics Committee (approval number: 63, date: 24.02.2025), and written informed consent was obtained from all participants. The principles of the Declaration of Helsinki were adhered to throughout the research process.

Participants

Patients who had attended the Physical Medicine and Rehabilitation outpatient clinics for at least three months between March and November 2025, who presented with complaints of shoulder pain and limited movement, who were clinically diagnosed with AC, and who met the inclusion/exclusion criteria were invited to participate in the study.

Inclusion criteria were: age between 18–70 years; shoulder pain lasting at least 3 months with limited shoulder movement; magnetic resonance imaging of the affected shoulder performed within the last three months; complete blood count, C-reactive protein (CRP), fasting plasma glucose (FPG), and fasting lipid panel [triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol]; and 25(OH)D and vitamin B12 levels measured within the last three months. Exclusion criteria were: a history of shoulder surgery or shoulder trauma; diagnosis of DM or pre-DM; use of triglyceride-lowering medication (statins, fibrates, omega-3, thiazolidinediones); thyroid disease (thyroidectomy, autoimmune thyroiditis, or thyroid dysfunction); pregnancy; acute inflammation; history of malignancy; alcohol use; chronic kidney disease or active infectious disease; viral hepatitis; and liver cirrhosis.

A total of 192 AC patients were evaluated during the study period. Of these, 159 were excluded from the study because they met exclusion criteria or had missing data (shoulder trauma: 15; DM: 83; use of lipid-lowering medication: 20; lack of current laboratory tests: 35; chronic kidney disease: 3; thyroid dysfunction: 17). The control group was recruited sequentially from the same outpatient clinics and consisted of individuals without shoulder-related symptoms who did not meet the exclusion criteria. Demographic, clinical, and laboratory data were recorded for all cases included in the study.

Calculation of Indices

The TyG index was calculated using the following formula:

$$\text{TyG index} = \text{natural log of} \\ ((\text{fasting triglycerides [mg/dL]} \times \text{FPG [mg/dL]}) / 2)$$

The following complete blood count parameters were used for the assessment of systemic inflammation:

$$\text{NLR} = \text{neutrophil count/lymphocyte count}$$

$$\text{PLR} = \text{platelet count/lymphocyte count}$$

$$\text{SII} = \text{platelet count} \times \text{neutrophil count/lymphocyte count}$$

Statistical Analysis

Descriptive statistics were expressed as the mean \pm standard deviation for continuous variables, and as the number of observations (n) for categorical variables. The normality of the data distribution was tested using the Shapiro–Wilk test. Continuous variables that were normally distributed were compared using the independent-samples t-test, whereas non-normally distributed variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-squared test or Fisher’s exact test.

To evaluate factors associated with the presence of AC, binary logistic regression analyses were conducted, and the results were reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Given the modest sample size, the number of covariates entered into each multivariable model was restricted, and covariates were selected a priori based on clinical relevance to reduce the risk of overfitting. A series of hierarchical models was constructed: Model 0 included age and BMI; Model 1 included LDL; Model 2 included FPG; and Model 3 included the TyG index. To minimise potential multicollinearity, collinearity diagnostics were assessed (e.g., tolerance and variance inflation factors). Because the TyG index is derived from FPG and triglycerides, closely related metabolic variables were not entered simultaneously the same model when appropriate. Model fit was evaluated using the Hosmer–Lemeshow goodness-of-fit test. A two-sided p value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 71 participants were included in the study (38 healthy, 33 AC). The mean age and BMI of the patient group were higher than those of the control group ($p<0.001$ and $p=0.001$, respectively). The healthy group had a higher level of education, whereas a higher proportion of the patient group were retired or housewives ($p=0.001$ and $p=0.047$, respectively). No significant differences in gender or smoking habits were found between the groups ($p=0.967$ and $p=0.908$, respectively). As the variables relating to hand dominance and affected side were only present in the patient group, no intergroup comparisons were made for these variables (see Table 1).

Compared with the healthy group, the patient group had higher FPG, LDL, and total cholesterol levels ($p=0.010$, $p=0.001$, and $p=0.049$, respectively). Additionally, the TyG index was significantly higher in patients ($p=0.020$). However, no significant differences were observed between the groups with respect to neutrophil, lymphocyte, platelet, NLR, PLR, SII, HDL, vitamin D, vitamin B12, and CRP values (all $p>0.05$). Triglyceride levels tended to be higher in the patient group, although the difference did not reach statistical significance ($p=0.071$; see Table 2).

Multivariate logistic regression analyses were performed to identify factors that predict the presence of AC. In Model 0, which included age and body mass index (BMI), age was an independent predictor of illness (aOR =1.094; 95% CI 1.036–1.155; $p=0.001$), whereas BMI was not significant ($p=0.111$). In Model 1, which included LDL, age remained significant (aOR =1.085; 95% CI 1.025–1.148; $p=0.005$), and LDL level was independently associated

with the presence of AC (aOR =1.019; 95% CI 1.001–1.037; $p=0.044$). In Model 2, when FPG was added to LDL, FPG did not show an independent association ($p=0.705$), but LDL retained its significance ($p=0.042$). In Model 3, when the TyG index was added alongside LDL, the TyG index did not demonstrate an independent association ($p=0.299$), while the association of LDL declined to borderline significance (aOR =1.017; 95% CI 0.999–1.036; $p=0.064$). Age remained a consistent independent predictor of the presence of AC in all models ($p\leq 0.013$) (Table 3).

DISCUSSION

This study examined whether the TyG index, lipid profile, and haematology-derived inflammatory indices differ between non-diabetic patients with AC and healthy controls, and whether these markers are associated with AC. Overall, our findings indicate that non-diabetic AC have a more adverse metabolic profile, whereas haematology-derived inflammatory indices were comparable to controls. In regression analyses, age remained associated with AC across adjusted models. Although LDL showed a significant association with AC in the age-adjusted analysis, this association was no longer statistically significant after adjustment for the TyG index, indicating that the LDL–AC association may overlap with insulin resistance-related metabolic factors rather than representing a stable independent risk factor.

DM, thyroid disorders, and dyslipidaemia have been reported as risk factors for AC.^{19,20} However, because dyslipidaemia commonly coexists with diabetes and thyroid disease, its independent contribution is difficult to isolate.^{19,21} Evidence is also mixed: Zhang et al.²¹ (including Mendelian randomisation analyses) found no significant association between circulating lipid levels and AC, whereas case-control data suggest that higher lipid levels may be related to AC, although triglycerides may not differ consistently from controls.^{7,22} In our cohort, LDL and total cholesterol were higher in patients with AC, whereas triglyceride levels were comparable between groups. Moreover, the LDL–AC association was evident only in age-adjusted analyses and was attenuated after accounting for the TyG index, underscoring the importance of insulin resistance-related metabolic context when interpreting lipid associations. Differences across studies may reflect design- and cohort-related factors, including medication use and residual confounding.

Hyperglycaemia may promote connective tissue changes via glycation and may be linked to heightened oxidative and inflammatory signalling.^{23,24} Several studies have associated higher FPG with AC risk,^{25,26} although much of this evidence derives from diabetic cohorts. In non-diabetic populations, higher FPG within the normoglycaemic range has also been

Table 1. Comparison of demographic and clinical characteristics between the healthy and patient groups

		Healthy (38)	Patient (33)	p value	ES	CI
Age (years) (mean ± SD)		42.08±12.43	56.73±11.11	<0.001 ^M	0.520	0.33–0.67
Sex (female), n		24	21	0.967 ^X	0.005	-0.228–0.238
BMI (kg/m ²) (mean ± SD)		25.42±3.42	28.33±4.20	0.001 ^M	0.410	0.19–0.59
Education	Primary and middle school, n	14	25	0.001 ^X	0.39	0.17–0.57
	High school, n	24	8			
Occupation	Retired/household, n	12	18	0.047 ^X	0.29	-
	Office work, n	20	8			
	Manual labor, n	6	7			
Hand dominans (right), n		-	32	-	-	-
Affected side	Dominant, n	-	21	-	-	-
	Non-dominant, n	-	12	-	-	-
Smoking status (current), n		12	10	0.908	0.014	-0.23–0.23
VAS activity (mean ± SD)		-	5.73±2.44	-	-	-
VAS rest (mean ± SD)		-	1.39±1.46	-	-	-
VAS night (mean ± SD)		-	4.91±2.71	-	-	-

Data are presented as mean ± SD for continuous variables and as n for categorical variables ^MMann–Whitney U test; ^Xchi-square test were used
 BMI: Body mass index, VAS: Visual analog scale, n: Number, CI: Confidence interval, ES: Effect size, SD: Standard deviation
 Variables related to hand dominance and the affected side were available only in the patient group; therefore, no between-group statistical comparisons were performed for these variables (–)

Table 2. Comparison of laboratory parameters between the healthy and patient groups

	Healthy (38)	Patient (33)	p value	ES	95% CI
Neutrophil (Neu) (×10 ⁹ /L)	4.16±1.09	4.39±1.30	0.408 ^t	0.196	-0.658–0.267
Lymphocyte (Lym) (×10 ⁹ /L)	2.39±0.80	2.42±0.98	0.845 ^M	0.023	-0.211–0.255
Platelets (Plt) (×10 ⁹ /L)	254.84±75.94	278.09±85.88	0.156 ^M	0.168	-0.068–0.386
Neu/Lym (NLR)	1.91±0.74	2.16±1.75	0.854 ^M	0.022	-0.213–0.254
Plt/Lym (PLR)	117.05±50.08	125.17±42.70	0.203 ^M	0.150	-0.370–0.080
SII (SIII)	488.36±245.09	559.18±336.19	0.170 ^M	0.163	-0.073–0.382
Fasting plasma glucose (mg/dL)	90.55±11.38	98.82±16.66	0.010 ^M	0.305	0.078–0.503
Triglycerides (mg/dL)	110.37±48.60	138.76±64.69	0.071 ^M	0.214	-0.020–0.426
HDL (mg/dL)	57.71±17.14	53.45±13.15	0.250 ^t	0.273	-0.191–0.736
LDL (mg/dL)	111.61±27.88	146.67±47.90	0.001^t	0.901	-1.383–(-0.413)
Total cholesterol (mg/dL)	188.42±34.71	211.67±57.79	0.049^t	0.491	-0.957–(-0.021)
Vitamin D (µg/L)	19.65±7.44	19.94±9.82	0.822 ^M	0.027	-0.208–0.258
Vitamin B12 (ng/L)	346.89±109.31	298.76±138.21	0.109 ^t	0.385	-0.085–0.852
TyG index	8.31±0.79	8.72±0.52	0.020 ^M	0.276	0.046–0.479
CRP (mg/L)	2.31±2.14	3.32±2.74	0.071 ^M	0.214	-0.020–0.426

Data are presented as mean ± SD. p values were obtained using Mann–Whitney U test (^M) or independent-samples t-test (^t), as appropriate. ES indicates ES (r for Mann–Whitney U; |Hedges' g| for t-test). 95% CI denotes the 95% CI of the ES
 NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TyG: Triglyceride–glucose index, CRP: C-reactive protein, SD: Standard deviation, ES: Effect size, CI: Confidence interval

associated with shoulder pathology and AC.^{27,28} Consistent with these reports, FPG levels were higher in our non-diabetic AC group than in controls.

The TyG index, a practical surrogate marker of insulin resistance derived from fasting glucose and triglyceride levels, is feasible for routine clinical use and epidemiological research.¹⁴ To our knowledge, this is the first study to assess TyG in patients with AC, and we observed higher TyG values in the AC group than in controls. Limited prior evidence supports a link between insulin resistance and AC severity, with higher homeostasis model assessment of insulin resistance reported to be associated with greater pain, disability, and reduced shoulder mobility.¹⁰ In our regression analyses, the lack of an independent TyG association may reflect limited statistical power and/or shared variance with correlated metabolic measures, underscoring the need for cautious, model-aware interpretation. Overall, these findings suggest that insulin resistance-related metabolic alterations may be relevant in AC even when diabetes is excluded.

Inflammation is implicated in AC pathogenesis, with cytokine-mediated processes contributing to fibrosis and abnormal tissue repair.²⁹⁻³¹ Haematology-derived indices such as NLR, PLR and SII are widely used as accessible,

non-specific markers of systemic inflammation,¹⁷ but data in AC are limited. Prior studies have reported differences in these indices across AC subtypes or related shoulder conditions.^{32,33} In our study, haematology-based inflammatory markers did not differ between patients with AC and controls, suggesting that any inflammatory signal in AC may not be reliably detected by peripheral blood indices. Given the measures' non-specificity and susceptibility to residual variability, limited power may also have contributed to null findings. Future studies incorporating cytokine-based biomarkers and/or tissue-level assessments may better characterise the inflammatory profile of AC.

This study has limitations. First, FPG was based on a single measurement, and repeated assessments would better account for within-person variability. Second, the single-centre design and modest sample size limited the number of covariates that could be included in multivariable models, thereby reducing the precision of estimates. Therefore, we used a streamlined, clinically informed modelling strategy and interpreted results as model-specific. Finally, laboratory values obtained within the preceding three months may have introduced variability due to timing differences relative to clinical evaluation.

Variable	Model 0: age + BMI	Model 1: age + BMI + LDL	Model 2: age + BMI + LDL + FPG	Model 3: age + BMI + LDL + TyG
Age (years) aOR (95% CI) p	1.094 (1.036–1.155) 0.001	1.085 (1.025–1.148) 0.005	1.080 (1.016–1.147) 0.013	1.079 (1.020–1.141) 0.008
BMI (kg/m²) aOR (95% CI) p	1.129 (0.973–1.310) 0.111	1.101 (0.947–1.281) 0.211	1.100 (0.945–1.280) 0.217	1.091 (0.936–1.271) 0.264
LDL (mg/dL) aOR (95% CI) p	—	1.019 (1.001–1.037) 0.044	1.019 (1.001–1.037) 0.042	1.017 (0.999–1.036) 0.064
FPG (mg/dL) aOR (95% CI) p	—	—	1.008 (0.967–1.051) 0.705	—
TyG index aOR (95% CI) p	—	—	—	1.836 (0.583–5.782) 0.299

Dependent variable: patient =1, healthy =0. aOR: Adjusted odds ratio, CI: Confidence interval. BMI: Body mass index, LDL: Low-density lipoprotein, FPG: Fasting plasma glucose, TyG: Triglyceride–glucose index.

CONCLUSION

These findings support consideration of a broader immunometabolic perspective in AC. In clinical practice, evaluating and addressing metabolic risk, particularly insulin resistance–related profiles, may be relevant even in non-diabetic patients and could inform holistic management beyond symptomatic treatment. Further research is needed larger longitudinal studies incorporating direct measures of insulin resistance and more specific inflammatory biomarkers to confirm these associations and clarify the underlying mechanisms.

Ethics

Ethics Committee Approval: Approval was obtained from the Univeristy of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu Ethics Committee (approval number: 63, date: 24.02.2025).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.E.Z., Z.E.E., S.A., E.D., M.Z., Concept: D.E.Z., S.A., Ö.K., M.Z., Design: D.E.Z., S.A., Ö.K., Data Collection or Processing: D.E.Z., Z.E.E., S.A., E.D., M.Z., Analysis or Interpretation: D.E.Z., Z.E.E., S.A., E.D., Ö.K., M.Z., Literature Search: D.E.Z., Z.E.E., S.A., E.D., M.Z., Writing: D.E.Z., E.D., Ö.K., M.Z.

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