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RESEARCH ARTICLE

Evaluation of Serum Lipid Profile as a Predictive Biomarker for Survival in Gastrointestinal Cancer Patients

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ABSTRACT

Objective: Altered lipid metabolism is increasingly recognized as a hallmark of cancer progression and may serve as a prognostic biomarker. While individual lipid components such as total cholesterol, LDLc, HDLc, and triglyceride have been evaluated in various malignancies, their prognostic relevance in gastrointestinal (GI) cancers remains unclear. This study aimed to assess the association between baseline lipid profiles and overall survival (OS) in GI cancer patients.

Materials and Methods: A retrospective analysis was conducted on 103 patients with histologically confirmed gastric, colorectal, rectal, or esophageal cancer treated between January 2024 and March 2025. Pre-treatment fasting lipid profiles, including total cholesterol, LDLc, HDLc, and triglyceride, were recorded. Optimal cut-off values were determined by receiver operating characteristic analysis, and OS was analyzed using Kaplan–Meier survival curves and log-rank tests.

Results: At a median follow-up of 22 months, 26 patients (25.2%) had died. Low baseline total cholesterol (<135 mg/dL), LDLc (<76.5 mg/dL), and HDLc (<40 mg/dL) were each significantly associated with reduced median OS (all p<0.01). Triglyceride levels did not significantly correlate with survival (p=0.400). Cancer type, stage, liver metastasis, sex, and diabetes status showed no significant association with OS.

Conclusion: Lower baseline total cholesterol, LDLc, and HDLc levels predict worse survival in GI cancer patients, highlighting the prognostic relevance of lipid metabolism. Routine lipid profiling may serve as an accessible tool for risk stratification in oncology. Prospective studies are warranted to validate these findings and explore lipid modulation as a therapeutic adjunct.

Keywords: Cholesterol, gastrointestinal cancer, HDLc, lipid profile, LDLc, triglyceride

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INTRODUCTION

Lipid metabolism plays an important role in cancer biology and systemic health. Dyslipidemia, involving changes in serum lipids like total cholesterol, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), and triglyceride, is recognized as a metabolic issue and potential prognostic factor in cancer.[1–2] In cancers such as colorectal, gastric, and hepatocellular, serum lipid changes relate to tumor progression, immune response, and inflammation, indicating baseline lipid profiles may have prognostic value.[3]

Cholesterol is crucial for maintaining cell membrane integrity, supporting hormone production, and facilitating intracellular signaling, functions that are vital for the growth and survival of cancer cells.[4] It facilitates lipid raft formation, clustering signaling molecules like receptor tyrosine kinases, and activating oncogenic pathways such as PI3K/AKT and MAPK.[5,6] Additionally, hypocholesterolemia may reflect malnutrition, cancer-related cachexia, or high tumor burden, particularly in gastrointestinal (GI) malignancies. A large nationwide cohort study by Lim et al.[7] demonstrated

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that lower serum cholesterol levels were inversely associated with gastric cancer risk among postmenopausal women, highlighting the potential role of cholesterol as a biomarker linked to cancer susceptibility and progression.

HDLc exerts protective anti inflammatory and antioxidant effects by removing cholesterol from tissues, modulating cytokines, and reducing oxidative stress.[8,9] LDLc may promote tumor growth by supplying cholesterol for dividing cells and membrane synthesis.[10] Disrupted HDLc and LDLc balance links to higher cytokines, endothelial dysfunction, and tumor angiogenesis, leading to poorer prognosis.[11,12] Thus, low HDLc and LDLc levels may indicate the host's metabolic and tumor microenvironment status, affecting survival. On the other hand, studies have shown that reduced lipid levels are linked to chronic inflammation, with elevated IL-6 and TNF-α suppressing hepatic lipoprotein production and increasing lipoprotein catabolism, potentially worsening prognosis by promoting tumor growth.[13,14]

Likewise, Gu et al.[15] (n=1,303) found that a higher preoperative HDLc/LDLc ratio was independently predictive of improved progression-free survival (HR 0.65; 95% CI 0.50–0.84; p=0.001) and overall survival (OS) (HR 0.60; 95% CI 0.45–0.80; p<0.001) in resectable colorectal cancer patients. Similarly, Tao et al.[16] demonstrated that lower serum HDLc levels were significantly correlated with larger tumor size (>5 cm) and advanced stage (p<0.01), and that elevated expression of cholesterol metabolism genes such as LDLcR (HR 3.12), ABCA1 (HR 1.66), and OSBPL1A (HR 1.38) independently predicted poorer disease-free survival. In a comprehensive meta-analysis by Zhou et al.,[17] low serum HDLc and total cholesterol were significantly associated with poorer OS across various malignancies, with the strongest effects observed in GI cancers. In a large cohort of 59,217 newly diagnosed cancer patients, Kim et al.[18] demonstrated a U shaped relationship between baseline total cholesterol and LDLc levels and all cause mortality. Specifically, both very low total cholesterol (≤97 mg/dL; aHR 1.54, 95% CI 1.43–1.66) and very low LDLc (≤57 mg/dL; aHR 1.38, 95% CI 1.14–1.68) were independently associated with increased risk of death.

In a comprehensive meta-analysis of 156 studies including gastric, colorectal, and hepatocellular carcinoma patients, Peng et al.[19] found that higher HDLc, TC, and ApoA1 levels were significantly associated with improved OS and DFS. Notably, LDLc and TG levels did not show consistent prognostic value. Conversely, the relationship between hypertriglyceridemia and cancer prognosis remains inconsistent. Some studies have reported that elevated triglyceride levels are associated with worse survival outcomes, potentially reflecting the complex interplay between lipid metabolism, metabolic syndrome, insulin resistance, and cancer-related cachexia. For example, Lee et al.[20] found that in terminal cancer patients, high triglyceride levels were independently linked to shorter survival, particularly when combined with low LDLc levels, suggesting that altered lipid metabolism may reflect both tumor-driven catabolic processes and systemic metabolic dysfunction.

Most studies on lipids in GI cancers are limited by narrow focus and lack of survival-optimized thresholds, leaving the prognostic value of major lipid parameters inadequately defined. The present study aims to examine the prognostic significance of baseline lipid profile parameters, including total cholesterol, LDLc, HDLc, and triglyceride, on OS in patients with GI cancers. Using a retrospective cohort design with receiver operating characteristic (ROC)-derived cut-off values and survival analysis, this study seeks to determine whether lipid abnormalities act as modifiable prognostic markers that can aid in risk stratification and guide future therapeutic strategies.

MATERIALS and METHODS

Study Design and Settings

This retrospective cohort study included patients diagnosed with GI cancers who presented to the medical oncology outpatient clinic of our hospital between 1 January 2024 and 31 March 2025. Patient data were obtained from the institutional electronic medical record system. Baseline demographic and clinical characteristics, including age, sex, tumor type (gastric, esophageal, colon, or rectal), stage at diagnosis, presence of liver metastases, and comorbid conditions such as diabetes mellitus and hypertension, were systematically recorded.

The exclusion criteria were as follows: history of any other malignancy, use of lipid-lowering medications (including statins, fibrates, ezetimibe, omega-3 fatty acids, or PCSK9 inhibitors), presence of active infection or acute inflammatory conditions at the time of diagnosis, known familial hypercholesterolemia or other genetic dyslipidemia syndromes, uncontrolled endocrine or metabolic diseases affecting lipid metabolism (such as hypothyroidism or nephrotic syndrome), chronic kidney disease stage ≥3 (eGFR <60 mL/min/1.73 m^2), chronic liver disease, current use of corticosteroids, immunosuppressive drugs, or hormonal agents known to interfere with lipid levels, prior initiation of cancer treatment before lipid measurement, and incom-

plete or missing clinical or laboratory data. A total of 103 patients were included in the final cohort for analysis.

Ethics Approval and Consent to Participate

This study was carried out in compliance with the Declaration of Helsinki. Informed consent was obtained from all patients or their caregivers. The Local Ethics Committee of Istanbul Medipol University approved the study (decision date: 19.06.2025, number: E-10840098-202.3.02-4097).

Lipid Profile Measurement

Fasting blood samples were obtained at cancer diagnosis, prior to any oncologic treatment, following an overnight fast of ≥8 hours. Serum lipid levels, including total cholesterol, LDLc, HDLc, and triglyceride, were measured using enzymatic colorimetric methods on the Roche Cobas 8000 analyzer. All assays were performed in the central biochemistry lab per institutional protocols. Lipid parameters were categorized as "low" or "high" based on cohort-specific ROC-derived cut-offs for OS: 135 mg/dL (total cholesterol), 76.5 mg/dL (LDLc), 40 mg/dL (HDLc), and 150 mg/dL (triglyceride).

Outcomes

The primary outcome was the association between baseline lipid parameters (total cholesterol, LDLc, HDLc, and triglyceride) and OS, defined as the time from diagnosis to death or last follow-up. Secondary analyses assessed OS across cancer types and by liver metastases, sex, diabetes status, and disease stage.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient demographics and clinical characteristics. The normality of distribution for continuous variables was assessed using the Kolmogorov–Smirnov test. ROC curve analysis was conducted to evaluate the predictive value of lipid profile parameters for OS, with area under the curve (AUC) and 95% confidence intervals (CI) reported. Kaplan–Meier survival curves were constructed to estimate OS, and group differences were tested using the log-rank (Mantel–Cox) test. OS was defined as the time from the date of cancer diagnosis to the date of death or last available follow-up. Median OS and corresponding 95% CIs were calculated. A two-sided p-value of less than 0.05 was considered statistically significant. Optimal cut-off values were determined by ROC analysis using the Youden index to maximize the sum of sensitivity and specificity. Pairwise comparisons between cancer types were evaluated using a chi-square test where appropriate.

Table 1. Demographic and clinical characteristics of the patients

Patient characteristic	Value	
	n	%
Age, years	56 (39–81)	
Gender		
Female	50	48.5
Male	53	51.5
Cancer type		
Colorectal	39	37.9
Rectal	22	21.4
Gastric	24	23.3
Esophageal	18	17.5
Cancer stage		
Stage 1	6	5.8
Stage 2	26	25.2
Stage 3	32	31.1
Stage 4	39	37.9
Presence of hepatic metastasis	29	28.2
Exitus	26	25.2

RESULTS

The median age was 56 years (range: 39–81). The cohort consisted of 53 males (51.5%) and 50 females (48.5%). By cancer type, the cohort comprised 39 colorectal cancer patients (37.9%), 24 gastric cancer (23.3%), 22 rectal cancer (21.4%), and 18 esophageal cancer patients (17.5%). At diagnosis, 6 patients (5.8%) were in stage I, 26 (25.2%) in stage II, 32 (31.1%) in stage III, and 39 (37.9%) in stage IV. Comorbid diabetes mellitus was present in 26 patients (25.2%), and hypertension in 29 (28.2%). Liver metastases were documented in 29 patients (28.2%). At a median follow-up of 22 months, 26 patients (25.2%) had died. Key demographic and clinical features are summarized in Table 1.

Patients with low baseline total cholesterol levels (<135 mg/dL) had a markedly shorter median OS compared to those with higher levels (≥135 mg/dL). Specifically, at a median follow-up of 22 months, the median OS in the low total cholesterol group was 7.0 months (95% confidence interval [CI]: 0.0–14.5), while the median OS was not reached in the high total cholesterol group (indicating that more than half of the patients in this group were still alive at the end of the

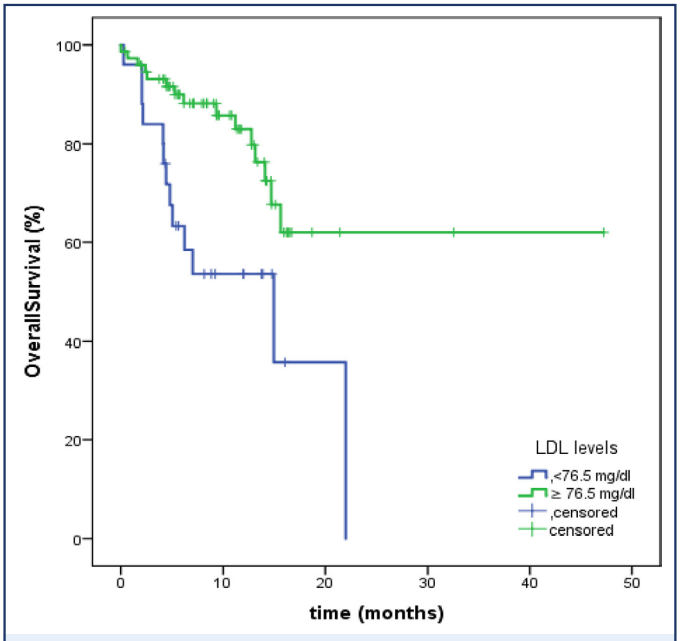

Figure 1. Kaplan–Meier overall survival curves for patients stratified by baseline LDLc levels (cut-off=76.5 mg/dL). The blue curve represents patients with LDLc <76.5 mg/dL and the green curve represents those with LDLc ≥76.5 mg/dL

LDLc: Low-density lipoprotein cholesterol

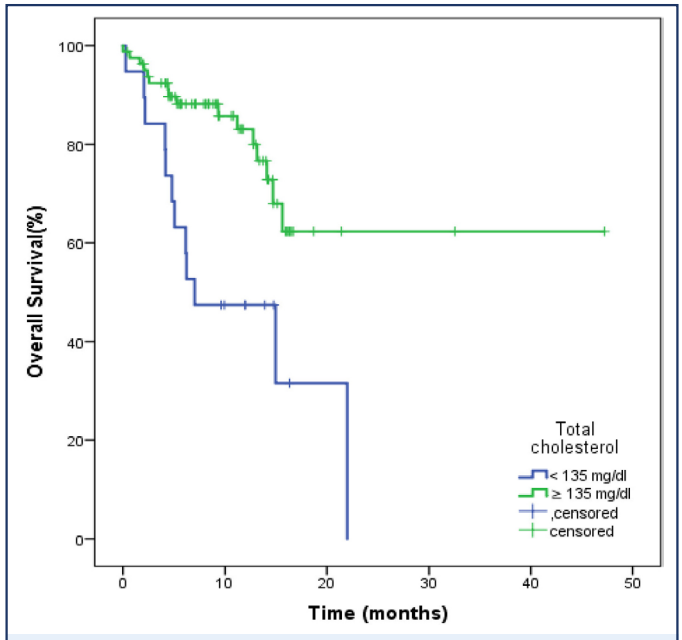

Figure 2. Kaplan–Meier overall survival curves for patients stratified by baseline total cholesterol levels (cut-off=135 mg/dL). The blue curve represents patients with total cholesterol <135 mg/dL, and the green curve represents those with total cholesterol ≥135 mg/dL

follow-up period). This difference was statistically significant (log-rank p=0.001). Similarly, patients with LDLc <76.5 mg/dL had a median OS of 14.97 months (95% CI: 2.76–27.17), compared to a not-reached median OS in those with LDLc ≥76.5 mg/dL (p=0.002). A comparable survival advantage was observed in patients with higher HDLc levels (≥40 mg/dL), as the median OS was not reached in this group, while it was 14.7 months (95% CI: 3.01–26.39) in the lower HDLc group (p=0.002). In contrast, triglyceride levels did not show a significant association with survival. When stratified by a cut-off value of 150 mg/dL, the median OS was 22.0 months (95% CI: 11.1–32.8) in the low triglyceride group (<150 mg/dL) and 14.7 months (95% CI: 13.4–16.0) in the high triglyceride group (≥150 mg/dL), but this difference did not reach statistical significance (log-rank p=0.4) (Figs. 1-3).

Despite no statistical significance, rectal cancer patients had a numerically shorter survival than those with colon cancer (χ^2=1.902, p=0.168), gastric cancer (χ^2=2.406, p=0.121), and esophageal cancer (χ^2=1.324, p=0.250), but these comparisons did not reach statistical significance. Similarly, the survival difference between colon and gastric cancers (χ^2=0.304, p=0.581) and between colon and esophageal cancers (χ^2=0.045, p=0.832) was not statistically significant.

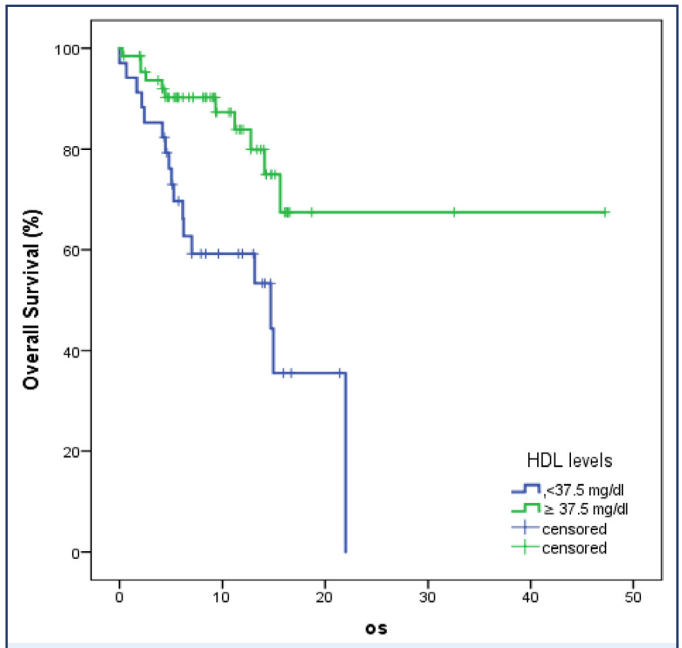

Figure 3. Kaplan–Meier overall survival curves for patients stratified by baseline HDLc levels (cut-off=40 mg/dL). The blue curve corresponds to patients with HDLc <40 mg/dL, and the green curve to those with HDLc ≥40 mg/dL

HDLc: High-density lipoprotein cholesterol

Cancer type was not a statistically significant determinant of OS (log-rank p>0.05); however, median OS was observed as follows: 25.6 months in gastric (95% CI: 18.7–32.6), 22.3 months in colon (95% CI: 16.1–28.5), 20.1 months in esophageal (95% CI: 13.9–26.2), and 17.4 months in rectal cancer (95% CI: 9.2–25.6).

Disease stage at diagnosis showed a non-significant trend toward poor OS in patients with stage IV disease compared to those with stage I–III (log-rank p=0.1).

Median OS was 19.3 months in patients with liver metastases (n=29, 28.2%) and 25.7 months in those without (n=52, 50.5%) (log-rank p = 0.087). Sex (female: n=50, 48.5%; male: n=53, 51.5%; p=0.438) and diabetes status (n=26, 25.2%; p=0.503) were not significantly associated with OS.

DISCUSSION

This study evaluated the prognostic significance of baseline lipid profile parameters, including total cholesterol, LDLc, HDLc, and triglyceride, on OS in patients with GI malignancies such as gastric, esophageal, colorectal, and rectal cancers. This concept is further supported by the comprehensive review of Pavlova and Thompson,[21] who emphasized that tumor-specific alterations in lipid metabolism, particularly shifts in fatty acid oxidation and cholesterol biosynthesis, represent key drivers of cancer progression and therapeutic resistance.

Several studies have highlighted the prognostic relevance of baseline lipid parameters in various GI malignancies, supporting the emerging view that dyslipidemia may influence not only cancer-related inflammation and nutritional status but also tumor progression and patient survival. For instance, Shen et al.[3] retrospectively evaluated 358 gastric cancer patients and found that patients with low preoperative HDLc (<54.2 mg/dL) exhibited deeper tumor invasion, more nodal metastasis, and advanced stage at presentation (p<0.05), suggesting a link between hypolipidemia and tumor aggressiveness, albeit without significant impact on OS.

Similarly, a comprehensive meta-analysis by Yang et al.[22] evaluated more than 15,000 non-metastatic colorectal cancer patients across 20 cohort studies and concluded that higher baseline HDLc levels were significantly associated with improved disease-free and OS (RR 0.86; 95% CI 0.77–0.97). In esophageal squamous cell carcinoma, Chen et al.[23] retrospectively analyzed 214 patients undergoing esophagectomy and found that low preoperative LDLc (<3.23 mmol/L, ~125 mg/dL) correlated with more advanced tumor stage. Multivariate analysis showed these patients had significantly shorter survival: median DFS was 17.7 vs. 55.3 months and median OS was 25.8 vs. 60.4 months for low versus high LDLc groups (p<0.001). The proposed mechanism involves HDLc's role in modulating oxidative stress and suppressing inflammation within the tumor microenvironment.

In a retrospective cohort study comprising 712 patients who underwent curative resection for colorectal cancer, Chen et al.[24] investigated the prognostic significance of preoperative serum triglyceride levels. Patients were stratified based on their preoperative TG concentrations into low and high groups. The survival outcomes were analyzed using multivariate Cox proportional hazards models, adjusting for potential confounders including tumor stage, BMI, and systemic inflammatory markers.

Their findings demonstrated that higher preoperative triglyceride levels were independently associated with both improved OS and disease-free survival (DFS). This suggests that adequate lipid reserves may play a protective role in sustaining metabolic homeostasis and energy supply during cancer progression. Furthermore, these results align with the broader concept that lipid metabolism is intricately linked to tumor biology and host resilience, highlighting the potential prognostic relevance of metabolic biomarkers in oncological outcomes.[24]

Recent high-quality retrospective studies have provided compelling evidence that serum lipid profiles carry prognostic value in GI cancers. For instance, Nam et al.[25] conducted a retrospective analysis on esophageal squamous cell carcinoma (ESCC) patients and found that lower preoperative LDLc levels were significantly correlated with poorer OS, presumably due to LDLc's role in maintaining cell membrane structure and supporting immune competence. For gastric cancer, Pih et al.[26] analyzed patient lipid profiles and reported that individuals with low HDLc and/or high LDLc/HDLc ratios exhibited more advanced disease stages and poorer prognosis, supporting the notion that dysregulated lipid transport may exacerbate tumor progression. In a retrospective study, Zhang and colleagues investigated the prognostic value of lipid profiles in 306 patients with esophageal squamous cell carcinoma undergoing curative esophagectomy. They evaluated preoperative serum lipid levels and demonstrated that low LDLc concentrations were independently associated with worse OS, even after adjusting for tumor stage and systemic inflammation, suggesting that LDLc plays a critical role in maintaining membrane stability and supporting immune competence in cancer patients.[27]

Our findings revealed that lower levels of total cholesterol, LDLc, and HDLc at diagnosis were significantly associated

with reduced OS. Specifically, patients with total cholesterol <135 mg/dL had a median OS of 7.0 months, while the median OS was not reached in those with higher levels (≥135 mg/dL). Similarly, patients with LDLc below 76.5 mg/dL and HDLc below 40 mg/dL had markedly shorter survival times compared to those with higher levels in each category. In contrast, triglyceride levels did not show a statistically significant association with OS.

In our cohort, OS did not differ significantly across GI cancers, yet rectal cases fared worst. Sánchez Martínez et al.[28] demonstrated in colon cancer cell models and clinical samples that overexpression of ACSL1/4 and SCD enzymes activates epithelial–mesenchymal transition, enhances invasive behavior, and correlates with poor outcomes in stage II colon cancer patients, suggesting that dysregulated lipid metabolism may similarly contribute to aggressive biology in rectal tumors.

In our cohort, stage IV disease showed a non-significant OS disadvantage versus stage I–III (p=0.109). Surveillance, epidemiology, and end results (SEER) program data cite 5-year survival rates of 91.5%, 73.4%, and approximately 15% for localized, regional, and distant colorectal cancer.[29,30] In metastatic gastric cancer, median OS has been reported as 6–13 months, whereas resectable stages yield 25–40 months, according to international consensus data.[31,32] Small early-stage patient numbers, a low number of events, and biologic/treatment heterogeneity likely underpowered our analysis, underscoring the need for larger, stage-balanced cohorts.[33]

Previous studies have consistently indicated that liver metastases significantly worsen OS in GI malignancies. However, Engstrand et al.[34] reported no statistically significant difference in OS between patients with synchronous versus metachronous liver metastases in colorectal cancer, suggesting that the timing of hepatic spread may be less important than its mere presence. In contrast, Sun et al.,[35] using SEER data on newly diagnosed gastric cancer patients with liver metastases, found median OS to be only 4.0 months in untreated individuals versus 12.0 months in those receiving multimodal therapy, emphasizing the poor prognosis associated with hepatic involvement and the potential benefits of treatment. In line with these findings, median OS was 19.3 months in patients with liver metastases (n=29, 28.2%) and 25.7 months in those without (n=52, 50.5%) (log-rank p=0.087) in our cohort. Although the difference did not reach statistical significance, likely due to sample size limitations, the trend aligns with prior literature suggesting the adverse prognostic impact of hepatic dissemination. Sex (female: n=50, 48.5%; male: n=53, 51.5%; p=0.438) and diabetes status (n=26, 25.2%; p=0.503) were not significantly associated with OS, consistent with meta-analyses indicating only modest or non-significant survival effects of these variables in GI cancers. These observations suggest that, in the context of GI malignancies, metastatic burden, particularly liver involvement, may exert a stronger influence on survival outcomes than baseline demographic or metabolic factors.

Our study has several limitations. As a retrospective, single-center analysis, it might introduce selection bias and limited generalizability. Lipid parameters were measured once before cancer treatment, preventing assessment of changes over time. We also did not collect data on diet, nutrition, BMI, or genetics that could influence lipid metabolism and outcomes. The study's observational nature means causality cannot be confirmed. Additionally, progression-free and recurrence-free survival were not assessed due to the inclusion of patients across all disease stages (I–IV), making OS the primary endpoint. However, with longer follow-up, including progression-free survival and relapse-free survival could offer useful prognostic insights. Additionally, inflammatory markers such as C-reactive protein or interleukin-6 (IL-6) were not assessed, which might have further clarified the role of systemic inflammation in lipid alterations.

Even with its retrospective, single-center scope and modest sample size, this study is the first to apply survival-optimized lipid cut-offs across four major GI cancers, showing that low baseline total cholesterol, LDLc, and HDLc reliably flag poorer OS By providing clinically actionable thresholds derived from routine blood tests, it supplies a practical risk-stratification tool and builds a rationale for prospective trials of lipid-modulating strategies in GI oncology. Furthermore, routine assessment of serum lipid profiles may aid in early risk stratification, particularly in resource-limited oncology settings, due to its accessibility and low cost.

CONCLUSION

Our study demonstrates that lower baseline levels of total cholesterol, LDLc, and HDLc are significantly associated with reduced OS in patients with GI cancers. These findings suggest that lipid profile parameters, particularly cholesterol-related indices, may serve as simple and accessible prognostic biomarkers. Prospective studies are needed to confirm these associations and to explore their potential role in individualized cancer management.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Medipol University Non-interventional Clinical Research Ethics Committee (No: E-10840098-202.3.02-4097, Date: 19/06/2025).

Informed Consent: Informed consent was obtained from all participants.

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