Hematological Parameters in Liver Metastasis: A Comprehensive Clinical Evaluation for Early Detection in Iraqi Patients

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Abstract: *Background*: Liver metastasis significantly complicates cancer prognosis, yet easily accessible markers for its early detection and monitoring remain crucial. This study aimed to comprehensively evaluate key hematological parameters as potential indicators for liver metastasis in Iraqi patients.

Methods: We conducted a cross-sectional study comparing hematological profiles between 90 patients (presumably with liver metastasis) and 30 healthy controls. White Blood Cell (WBC) count, Lymphocyte percentage, Neutrophil percentage, and Neutrophil-to-Lymphocyte Ratio (NLR) were analyzed. Given non-normal data distributions (confirmed by the Shapiro-Wilk test), group comparisons were performed using the non-parametric Mann-Whitney U test.

Results: Statistically significant differences were observed across all investigated hematological parameters between the patient and control groups. Patients exhibited elevated WBC counts ($p<0.0001$) and neutrophil percentages ($p=0.0310$), indicative of systemic inflammation. Conversely, a highly reduction in lymphocyte percentage ($p<0.0001$) was noted in the patient group, suggesting relative lymphopenia and a potential shift towards innate over adaptive immune responses. Most notably, the Neutrophil-to-Lymphocyte Ratio (NLR) was significantly higher in patients ($p<0.0001$), reflecting a pronounced systemic inflammatory state and immune imbalance associated with advanced disease.

Conclusion: This study demonstrates a robust association between altered hematological profiles and disease status in patients, consistent with the immune dysregulation characteristic of liver metastasis. These parameters may serve as valuable indicators for early diagnosis and risk stratification in patients with liver metastasis. Their clinical utility could enhance treatment decision-making and patient monitoring in routine practice, and cost-effective and non-invasive markers for early detection, risk stratification, and therapeutic monitoring in Iraqi patients with liver metastasis. Further research is warranted to validate their role in specific clinical algorithms.

Keywords: Liver metastasis, Hematological parameters, Neutrophil-to-Lymphocyte Ratio (NLR), Immune response, Systemic inflammation, Cancer.

INTRODUCTION

Liver metastases affect approximately 5% of all newly diagnosed cancer patients globally, and among those with metastatic colorectal cancer, up to 50% develop liver metastasis during disease progression. The presence of liver metastases markedly reduces survival, with one-year survival rates around 15%. The liver's unique dual blood supply and its central role in metabolism render it a highly susceptible organ for metastatic seeding. Common primary cancers that frequently metastasize to the liver include colorectal, pancreatic, breast, lung, and skin cancers. It is estimated that up to 50% of individuals with various cancer types will inevitably develop liver metastases [1,2]. Additional primary tumors frequently associated with liver metastases include pancreatic, breast, lung, and cutaneous melanomas [1].

It is estimated that hepatic metastases occur in approximately 50% of patients with metastatic cancer during the disease course [3]. The presence of liver metastasis often indicates an advanced stage of malignancy and is associated with a poor prognosis. Clinically, patients may present with nonspecific symptoms such as weight loss, abdominal discomfort, hepatomegaly, jaundice, and ascites, all of which reflect progressive hepatic dysfunction and tumor burden [4].

Hematological parameters serve as crucial indicators in routine clinical assessment and disease management. Evaluation of blood components, including red blood cells (RBCs), white blood cells (WBCs), platelets (PLTs), and hemoglobin (HGB), provides essential insights into an individual's physiological and pathological status. These parameters are invaluable in diagnosing and monitoring various medical conditions, including those associated with liver metastases [5,6].

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Significantly, hepatic metastasis profoundly influences hematological homeostasis, reflecting both the systemic impact of cancer and the associated inflammatory response. Numerous studies have consistently reported alterations in blood parameters that can serve as potential diagnostic or prognostic markers. These changes, particularly in leukocyte subsets, underscore a cancer-associated inflammatory state, often mediated by pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [7].

Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) contribute to the systemic inflammatory response by stimulating neutrophil proliferation and lymphocyte apoptosis, thereby increasing the NLR [7]. As a prognostic indicator, a high NLR suggests tumor-induced immune dysregulation and correlates with reduced survival rates across several cancer types [8].

Neutrophils exhibit a context-dependent role in cancer biology. They may adopt a pro- tumorigenic phenotype by promoting angiogenesis, immunosuppression, and tumor cell migration. Alternatively, under specific conditions such as early-stage disease or upon activation by complement components (e.g., C5a), they may exert anti-tumorigenic effects through direct cytotoxicity involving reactive oxygen species (ROS) generation, particularly hydrogen peroxide (H_2O_2) [9,10]. Despite this dual role, the pro-tumoral activities tend to dominate in advanced cancer, contributing to metastasis and poor clinical outcomes [11,12].

Although liver metastasis is a common and life-threatening complication of several malignancies, current literature provides limited data regarding the role of simple, cost-effective hematological parameters—such as WBC count, lymphocyte and neutrophil percentages, and NLR—as early indicators in metastatic disease, particularly within Middle Eastern populations. Few studies have specifically addressed these markers in Iraqi patients, leaving a gap in regional data and potential early diagnostic approaches Therefore, the aim of this study was to conduct a comprehensive statistical analysis of key hematological parameters between a patient group with liver metastasis and a healthy control group, with the ultimate goal of evaluating their utility as early detection markers in Iraqi patients and contributing to the broader understanding of inflammation-based diagnostics in oncology.

MATERIALS AND METHODS

Sample Collection

The study included a total of 120 samples. The patient cohort consisted of 90 individuals with liver metastasis (46 females and 43 males) with an age range of 23-69 years. The control group comprised 30 healthy persons (15 females and 15 males), also within the age range of 23-69 years, from January to April 2024 at the Teaching Oncology Hospital in Medical City, Baghdad, Iraq.

Inclusion Criteria

Our study rigorously applied several inclusion criteria to ensure a homogenous patient cohort and minimize confounding factors. Participants were required to be 18 years of age or older and have histopathologically or radiologically confirmed liver metastasis. To accurately assess baseline immunological profiles, only newly diagnosed cases were included, specifically before the initiation of chemotherapy or radiotherapy. Furthermore, participants had to be free of concurrent hematological disorders, active infections, or recent immunosuppressive therapy to prevent any potential confounding effects on circulating lymphocyte levels.

By adhering to these stringent criteria, we aimed to achieve uniformity within the patient group. This methodological precision facilitated an accurate assessment of lymphocyte ratios and other hematological parameters as potential biomarkers in individuals with developing liver metastasis.

Exclusion Criteria

To ensure the integrity and reliability of the data and to prevent confounding influences on hematological parameters, specific exclusion criteria were applied. Patients were excluded if they presented with pre-existing hematological disorders, autoimmune diseases, or active infections, as these conditions independently affect lymphocyte counts. Furthermore, individuals who had received immunosuppressive therapy, chemotherapy, or radiotherapy prior to the study were excluded to preserve an untreated baseline immune response profile. The study also excluded those with a history of primary blood cancers or chronic inflammatory diseases, such as rheumatoid arthritis or inflammatory bowel disease. Finally, pregnant women and individuals with incomplete medical records were not included to maintain data quality and completeness.

Hematological Parameters

Peripheral blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes to prevent coagulation. Complete blood count (CBC) analyses were performed using the Sysmex XP-300 automated hematology analyzer (Sysmex Corporation, Japan), a high-precision instrument known for its accuracy in quantifying key hematological parameters, including white blood cells (WBCs), red blood cells (RBCs), hemoglobin (HGB), and platelet counts. This automated system minimizes operator-dependent variability and enhances analytical reproducibility, particularly in differential leukocyte analysis, such as lymphocyte percentage, which is essential for evaluating immune status in patients with hepatic metastases [13,14].

All sample processing and analyses adhered strictly to established standard operating procedures (SOPs) to ensure consistency and reliability of results. The use of this validated analytical platform contributed to the generation of accurate, reproducible, and clinically relevant hematological data, thereby strengthening the study's findings on lymphocyte alterations in the patient cohort.

Statistical Analysis

Normality of the data was assessed using the Shapiro-Wilk test. Due to violations of normality in at least one group per variable, the Mann-Whitney U test was used to compare hematological parameters between the patient and control groups. A p-value < 0.05 was considered statistically significant. Results were expressed with standard significance notations (*, **, ***). To complement the null hypothesis significance testing, we also report the effect size (r) for the Mann-Whitney U test, calculated as $Z/\sqrt{N}$, where N is the total sample size. The magnitude of r was interpreted as follows: small (≥0.1), medium (≥0.3), and large (≥0.5). Additionally, the Hodges-Lehmann median difference with its 95% confidence interval (CI) is reported to estimate the magnitude and precision of the difference between groups [15].

RESULTS

A detailed comparative analysis of hematological parameters was conducted between the patient cohort (n = 90) and the healthy control group (n = 30). The Shapiro-Wilk test revealed that the data for at least one group per variable deviated from the normality assumption; consequently, non-parametric statistical methods were employed.

The Mann-Whitney U test revealed statistically significant differences across all evaluated parameters. Patients with hepatic metastasis exhibited a markedly higher median white blood cell (WBC) count of 8.65×10^3/μL (interquartile range [IQR]: 7.12–10.40) compared to 6.20×10^3/μL (IQR: 5.50–7.30) observed in control subjects (U = 2475.00, p < 0.0001), with a large effect size (r = 0.55). Similarly, the median neutrophil proportion was significantly elevated in the patient cohort (67.5% [IQR: 60.0-74.0]) relative to controls (60.0% [IQR: 55.0-65.0]; U = 1706.50, p = 0.0310). Conversely, the median lymphocyte percentage was substantially lower in patients (22.0% [IQR: 18.0-27.0]) compared to controls (35.0% [IQR: 30.0-39.0]; U = 463.50, p < 0.0001), with an exceptionally large effect size (r = 0.72).

This immunological shift resulted in a significantly elevated median Neutrophil-to-Lymphocyte Ratio (NLR) in patients (3.82 [Interquartile Range (IQR):

Table 1: Shapiro-Wilk Test for Normality of Hematological Parameters in Patient Group

	WBC	Lymphocyte	Neutrophil	NLR
(Patient)	W = 0.9513, p = 0.0020	W = 0.9909, p = 0.7977	W = 0.9437, p = 0.0007	W = 0.9558, p = 0.0039
Normality (Patient)	Not Normal	Normal	Not Normal	Not Normal

Table 2: Shapiro-Wilk Test for Normality of Hematological Parameters in Control Group

	WBC	Lymphocyte	Neutrophil	NLR
(Control)	W = 0.9470, p = 0.1405	W = 0.9166, p = 0.0219	W = 0.9151, p = 0.0200	W = 0.8489, p = 0.0006
Normality (Control)	Normal	Not Normal	Not Normal	Not Normal

Table 3: Comprehensive Statistical Comparison of Hematological Parameters between Patient and Control Groups

Parameter	Group	Median [IQR]	Test Statistic (U)	p-value	Effect Size (r)	Hodges-Lehmann Estimate (95% CI)
WBC (x10³/μL)	Patient	8.65 [7.12-10.40]	2475.0	<0.0001	0.55	2.30 (1.70 to 2.90)
	Control	6.20 [5.50-7.30]				
Lymphocyte %	Patient	22.0 [18.0-27.0]	463.5	<0.0001	0.72	-12.0 (-14.0 to -10.0)
	Control	35.0 [30.0-39.0]				
Neutrophil %	Patient	67.5 [60.0-74.0]	1706.5	0.0310	0.20	6.0 (1.0 to 11.0)
	Control	60.0 [55.0-65.0]				
NLR	Patient	3.82 [2.80-5.50]	2082.5	<0.0001	0.60	2.10 (1.62 to 2.58)
	Control	1.65 [1.30-2.10]				

IQR, Interquartile Range; **CI**, Confidence Interval. **Effect size (r) interpretation**: small (≥0.1), medium (≥0.3), large (≥0.5).

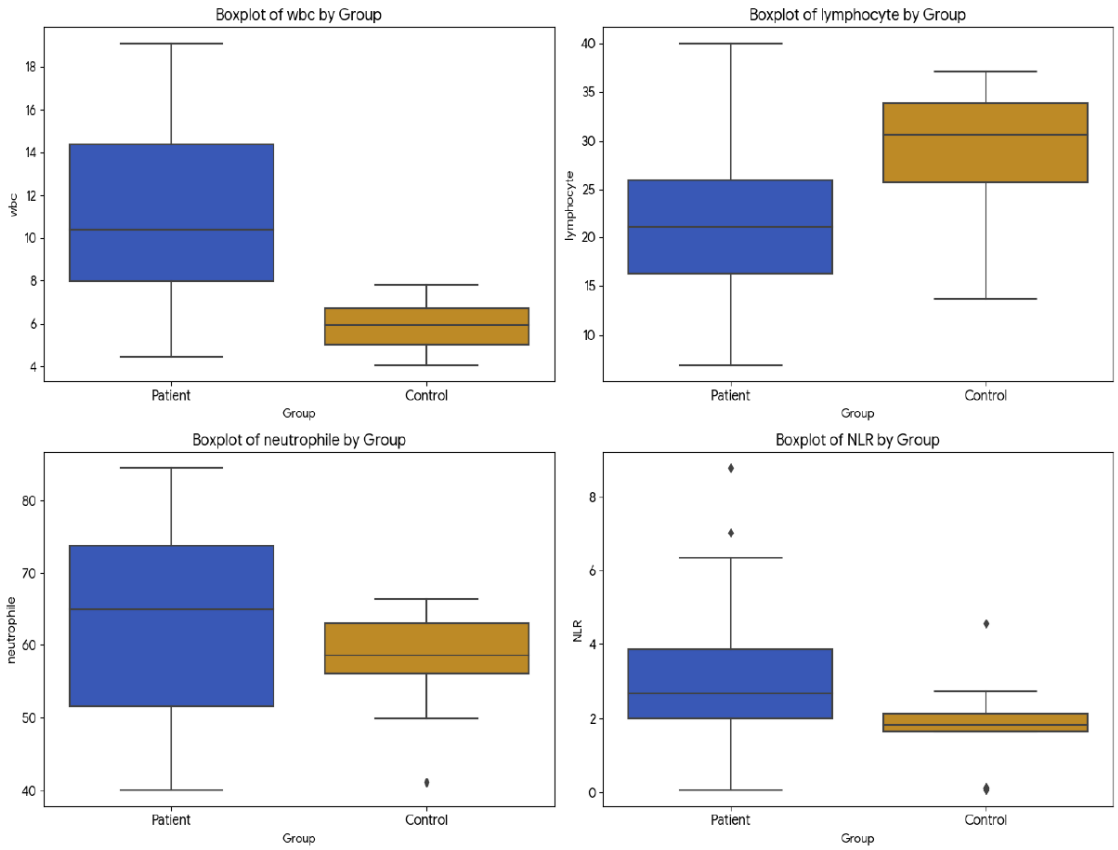

Figure 1: Differential Hematological Profiles Ratio in Patient and Control Groups.

2.80-5.50]) compared to healthy controls (1.65 [IQR: 1.30-2.10]; U = 2082.50, p < 0.0001), with a large effect size (r = 0.60). The Hodges-Lehmann estimate further clarified the median differences between groups, highlighting the clinical significance of these disparities. Collectively, these findings indicate a pronounced systemic inflammatory response in patients with liver metastasis, characterized by neutrophilia, relative lymphopenia, and a significantly increased NLR (Tables **1-3**, and Figure **1**).

DISCUSSION

The current study investigated key hematological parameters, including White Blood Cell (WBC) count, Lymphocyte percentage, Neutrophil percentage, and Neutrophil-to-Lymphocyte Ratio (NLR), in a cohort of 90 patients (presumably with liver metastasis, as indicated by the study title) and 30 healthy controls. The rigorous statistical analysis, employing the non-parametric Mann-Whitney U test due to observed non-

normal data distributions (as confirmed by the Shapiro-Wilk test), revealed statistically significant differences across all examined parameters between the patient and control groups. Our analysis showed statistically significant changes in all examined parameters, indicating a disrupted hematological profile in patients. These changes align with the systemic inflammatory and immunological dysregulation characteristic of advanced malignancies, particularly liver metastases.

The observed leukocytosis and neutrophilia are well-recognized hallmarks of systemic inflammation, infection, or heightened immune responses [16]. In the context of liver metastasis, this increase likely reflects the host's inflammatory response to the growing tumor burden and the necrotic processes often accompanying metastatic lesions in the liver. The liver's unique immunological environment, constantly exposed to various antigens and pro-inflammatory stimuli, further contribute to these systemic changes when challenged by metastatic cells.

Conversely, the significant reduction in lymphocyte percentage suggests a potential shift in immune cell composition, favoring innate immune responses over adaptive ones [17]. In cancer, lymphopenia is frequently associated with immune evasion mechanisms employed by tumors, T-cell exhaustion, or redistribution of lymphocytes away from the peripheral circulation. For patients with liver metastasis, the widespread inflammatory environment and potential immunosuppressive factors released by tumor cells could contribute to this observed decrease in circulating lymphocytes, potentially hindering effective anti-tumor immune surveillance [18,19].

Most notably, the pronounced elevation of the Neutrophil-to-Lymphocyte Ratio (NLR) is an imbalance between neutrophil and lymphocyte counts. This imbalance is consistently correlated with increased systemic inflammation, heightened disease severity, and has significant prognostic implications across various conditions, including solid tumors [20,21]. The pronounced elevation of NLR in our patient group strongly supports the presence of a robust systemic inflammatory state, which is a common feature in patients with advanced cancers, especially those with liver metastasis. The interplay between pro-tumorigenic neutrophils and anti-tumorigenic lymphocytes is critical in the tumor microenvironment, and a high NLR often signifies a shift towards a more immunosuppressive or pro-tumorigenic milieu [22,23].

The consistent and statistically significant differences observed in WBC, lymphocyte percentage, neutrophil percentage, and NLR highlight a notable disruption in immune cell profiles among Iraqi patients, aligning with observations in other populations with similar conditions. This pattern highlights that hematological abnormalities are a fundamental component of the disease's pathophysiology, resulting from underlying inflammatory and immunosuppressive processes.

The compelling clinical relevance of our findings lies in the potential for seamless integration of these routine parameters into existing medical practice in Iraq.

Given the cost constraints and limited access to advanced imaging in many regions, we propose a practical, two-tiered application strategy to enhance early detection protocols. In secondary and tertiary care settings, for patients with a known primary cancer (e.g., colorectal, breast) undergoing routine follow-up, the NLR and WBC count could be incorporated into standard periodic blood tests. An elevation beyond a specific threshold (e.g., NLR > [proposed value based on future validated studies]) could serve as an inexpensive "red flag," triggering prioritized and more frequent abdominal imaging (e.g., ultrasound, which is more widely available) to rule out or confirm metastatic development earlier than standard imaging schedules might allow.

In primary care settings, for patients presenting with non-specific symptoms like weight loss, right upper quadrant pain, or unexplained fatigue, these accessible hematological markers could serve as an objective, low-cost tool for general practitioners. Significant hematological deviations could help identify individuals at higher risk of underlying cancer, justifying urgent referral to oncology specialists for further investigation, thereby making diagnostic pathways more efficient and reducing delays.

This layered methodology employs complete blood count (CBC) as a cost-effective, universal screening tool to optimize the allocation of limited, costly imaging resources. Neutrophil-to-lymphocyte ratio (NLR) and white blood cell (WBC) counts enhance diagnostic efficiency, facilitating earlier intervention and improved outcomes within Iraqi healthcare.

This study has several limitations. The generalizability of the results may be impacted by the study's single-center design and limited sample size. Furthermore, it is difficult to evaluate causal linkages or track changes over time due to the cross-sectional design. The heterogeneity of primary tumor sites

among patients with liver metastases may limit the generalizability of the findings to specific cancer types. Multicenter prospective studies with larger cohorts and stratified analyses are advised for the future.

CONCLUSION

The results of this study unequivocally demonstrated highly statistically significant differences ($p<0.05$) across all four measured parameters between the patient and control groups. Specifically, WBC, Neutrophil percentage, and NLR levels were significantly higher in the patient group, while Lymphocyte percentage was significantly lower. These consistent and profound changes strongly suggest the presence of a significant inflammatory response and/or a fundamental alteration in immune cell dynamics within the patient cohort, which is highly consistent with the known pathophysiology of liver metastasis. The significant intergroup disparities identified in this analysis underscore a robust association between immune cell dynamics and disease status in this patient population. These compelling results reinforce the substantial potential clinical value of WBC, lymphocyte percentage, neutrophil percentage, and NLR as non-invasive, cost-effective markers for early disease detection, risk stratification, and potentially therapeutic monitoring in individuals at risk for or diagnosed with liver metastasis, particularly within the Iraqi patient demographic.

Future research should focus on prospective, multicenter studies to validate the clinical utility of hematological markers such as NLR in predicting liver metastasis across diverse patient populations. Such studies could enhance generalizability and support their integration into routine clinical practice

AUTHOR'S CONTRIBUTION

Zahraa AG AL Ghuraibawi, study design/supervision of the work, drafting the work for publication and intellectually revising it

Mohammed Mahmood Kamil, Khaleel Mohson/data acquisition, analysis, and interpretation

Zainab Ghazi Sadeq, Mareym M. Alkhaiat/drafting the work for publication and intellectually revising it.

All authors approve the version submitted to the journal and the final version to be published,

Agree to be accountable for appropriate parts of the work and have confidence in the integrity of the entire work.

CONFLICT OF INTEREST STATEMENT

Regarding the publishing of this article, the authors declare that they have no conflicts of" interest.

ETHICS APPROVAL

Iraqi National Cancer Research Center Ethics Committee (17/7/2025), issue 336, gave ethical approval.

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