

## Comparison of the Role of High Neutrophil to Lymphocyte Ratio with Leukocytosis in Diagnosing Acute Cholecystitis

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### ABSTRACT

**Objective:** To compare the diagnostic accuracy of high neutrophil-to-lymphocyte ratio levels versus leukocytosis in detecting acute cholecystitis.

**Study Design:** Cross-sectional validation study.

**Place and Duration of Study:** Department of General Surgery, Combined Military Hospital, Rawalpindi Pakistan, from Dec 2021 to Jun 2022.

**Methodology:** One hundred eighteen patients with the clinical diagnosis of acute cholecystitis were included in the study. Patients with neoplastic or autoimmune disease or ongoing chronic infections were excluded. All patients underwent a test for complete blood counts to document the total leucocyte count and the neutrophil-to-lymphocyte ratio. The diagnosis of acute cholecystitis was confirmed on contrast-enhanced computed tomography abdomen.

**Results:** The study sample had a mean age of  $46.56 \pm 13.78$  years, with 81 (68.6%) females. The total leucocyte count had a sensitivity of 67.1%, a specificity of 73.3% and a diagnostic accuracy of 69.5% for predicting the presence of acute cholecystitis. In contrast, the neutrophil to lymphocyte ratio, with a cut-off of 3, had a sensitivity of 73.7%, a specificity of 68.9% and a diagnostic accuracy of 71.2% in predicting the presence of acute cholecystitis using contrast-enhanced computed tomography as a gold standard.

**Conclusion:** Both total leucocyte count and the neutrophil to lymphocyte ratio were equally effective for diagnosing acute cholecystitis in clinically diagnosed patients.

**Keywords:** Acute cholecystitis, Leukocytosis, Neutrophil to lymphocyte ratio.

**How to Cite This Article:** Khalid MU, Ashraf MA, Zainab A, Rehman ZU, Sufyan M, Fatima F. Comparison of the Role of High Neutrophil to Lymphocyte Ratio with Leukocytosis in Diagnosing Acute Cholecystitis. *Pak Armed Forces Med J* 2023; 73(6): 1737-1740.

DOI: <https://doi.org/10.51253/pafmj.v73i6.8895>

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### INTRODUCTION

Acute cholecystitis affects 10-15% of the global adult population, accounting for most surgeons' practices.<sup>1</sup> In developing countries like Pakistan, the prevalence of this disease is on the lower end of the spectrum mentioned above, affecting 10.2% of the adult population and being more common in females.<sup>2</sup>

Diagnosis of acute cholecystitis is based on a combination of history, clinical examination, biochemical tests and imaging, with particular emphasis on imaging in the developed world.<sup>3,4</sup> While imaging modalities such as contrast-enhanced computed tomography abdomen are very useful in detecting acute cholecystitis, especially in developing its complications, they are not cost-effective or readily available in resource-poor settings.<sup>5,6</sup> Thus, the search is always on for surrogate signs or biochemical markers which may complement clinical impressions of the presence of

acute cholecystitis, which can cost-effectively establish a definitive diagnosis, and several biochemical markers have been proposed to fulfil this requirement, with varying degrees of success.<sup>7,8</sup>

Complete blood counts are performed routinely in patients with acute cholecystitis, and the neutrophil-to-lymphocyte ratio can be quickly calculated from this test; the ratio is thought to be an accurate predictor of the presence of systemic inflammation.<sup>9</sup> The ratio has been useful in predicting severity in cases with acute cholecystitis.<sup>10</sup>

Acute cholecystitis is a commonly encountered surgical malady in the emergency department. Rapid screening of cases using a simple, readily available and cheap test can make managing the disease more efficient without resorting to expensive and expertise-intensive imaging modalities. The neutrophil to lymphocyte ratio has been proposed to be such a test; this study was conducted to ascertain the role, if any, this test could have when used to determine the presence of acute cholecystitis based on clinical suspicion.

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Received: 17 Jun 2022; revision received: 21 Sep 2022; accepted: 30 Sep 2022

**METHODOLOGY**

The cross-sectional validation study was conducted at Department of General Surgery, Combined Military Hospital, Rawalpindi Pakistan December 2021 to June 2022 via non-probability consecutive sampling. The Ethical Committee of Combined Military Hospital, Rawalpindi, approved the study (ERC/IRB CMH Rwp Ser no 244 dated 11-06-22). The WHO sample size calculator was used to calculate the sample size, keeping an expected sensitivity of 70.5%, expected specificity of 70.0%, expected prevalence of 40.5%.<sup>11</sup>

**Inclusion Criteria:** Patients of either gender, aged 18 to 70 years, with a clinical suspicion of acute cholecystitis were included after informed consent.

**Exclusion Criteria:** Patients who had suffered from malignancies, trauma, autoimmune disease, concurrent chronic infections or had received immunomodulatory drugs within the past four weeks were excluded.

Patients received an initial evaluation via a history and clinical examination on enrollment. All patients then underwent blood sampling by a qualified phlebotomist with at least two years of experience in the field. Complete blood counts were performed on the samples via a calibrated and control-tested Sysmex XP-300 Haematology Analyzer. A neutrophil-to-lymphocyte ratio of 2.8 or greater was considered to be elevated and suggestive of the presence of acute cholecystitis. At the same time, a total leucocyte count of greater than  $11.0 \times 10^3/\mu\text{L}$  was also considered to be indicative of the same. The diagnosis was confirmed on the contrast-enhanced computed tomography abdomen finding of a dilated, thickened gallbladder, with peri-cholecystic fat stranding (Figure), reported by a consultant radiologist with a minimum of five years post-fellowship experience.



**Figure: Contrast-Enhanced Computed Tomography of Abdomen showing Acute**

Data was analyzed using the Statistical Package for the Social Sciences version 26.0. Mean and SD were

calculated for quantitative variables. Qualitative variables were recorded as frequency and percentage. A 2x2 contingency table was constructed to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of both neutrophils to lymphocyte ratio and total leucocyte count in detecting the presence of acute cholecystitis.

**Table-I: Study Results according to Gender (n=118)**

Variables	Male	Female	p-value
Gender	37(31.4%)	81(68.6%)	-
Age (years)	44.59±14.82	47.46±13.28	0.297
Body Mass Index (kg/m <sup>2</sup> )	29.24±2.66	29.07±2.70	0.749
<b>Comorbidities</b>			
None	15(40.6%)	49(60.5%)	0.226
Diabetes Mellitus Alone	9(24.3%)	17(21.0%)	
Hypertension Alone	10(27.0%)	9(11.1%)	
Ischaemic Heart Disease	1(2.7%)	1(1.2%)	
Chronic Obstructive Pulmonary Disease	1(2.7%)	4(5.0%)	
Diabetes Mellitus Plus Hypertension	1(2.7%)	1(1.2%)	
Total Leucocyte Count (x 10 <sup>9</sup> /μL)	8.95±3.05	16.62±6.13	<0.001
Raised Total Leucocyte Count	10(27.0%)	63(77.8%)	<0.001
Neutrophil Count (x 10 <sup>9</sup> /μL)	5.85±2.46	13.36±6.16	<0.001
Lymphocyte Count (x 10 <sup>9</sup> /μL)	2.80±0.56	2.96±0.55	0.139
Neutrophil to Lymphocyte Ratio	2.01±0.48	4.73±2.91	<0.001
High Neutrophil to Lymphocyte Ratio	1(2.7%)	56(69.1%)	<0.001
Computed Tomography Positive	12(32.4%)	49(60.4%)	0.005

**RESULTS**

We studied 118 patients, of which 81 (68.6%) were female, with a mean age of 46.56±13.78 years. The mean body mass index of the patients was 29.12±2.68 kg/m<sup>2</sup>. 26(22%) had diabetes mellitus, 19(16.1%) had hypertension, ischaemic heart disease was present in 2(1.7%), while 5(4.2%) had pre-existing chronic obstructive pulmonary disease & 2(1.7%) had concurrent diabetes mellitus and hypertension. The mean total leucocyte count was  $14.21 \pm 6.43 \times 10^9/\mu\text{L}$ , with 73(61.9%) having a raised count. The mean neutrophil count, mean lymphocyte count and mean neutrophil to lymphocyte ratio for the study sample were  $11.01 \pm 6.33 \times 10^9/\mu\text{L}$ ,  $2.91 \pm 0.55 \times 10^9/\mu\text{L}$  and  $3.88 \pm 2.73 \times 10^9/\mu\text{L}$ , respectively. 57(48.3%) patients had a high neutrophil-to-lymphocyte ratio indicative of acute cholecystitis, while acute cholecystitis was present in 61(51.7%) patients based on contrast-enhanced computed tomography abdomen (Table-I).

Considering a ratio of the above three indicative of acute cholecystitis, the neutrophil to lymphocyte ratio had a sensitivity of 73.7%, a specificity of 68.9% and a diagnostic accuracy of 71.2%. That was similar to values for total leucocyte count, with a cut-off level of  $11.0 \times 10^9/\mu\text{L}$ , which had a sensitivity of 67.1%, a specificity of 73.3% and a diagnostic accuracy of 69.5%. The results for the different characteristics of both the total leucocyte count and the neutrophil-to-lymphocyte ratio are shown in Table-II.

**Table-II: Diagnostic Parameters**

Tests	Sensi-tivity	Speci-ficity	Positive Predictive Value	Negative Predictive Value	Diagnostic Accuracy
Total Leucocyte Count	67.1%	73.3%	80.3%	57.9%	69.5%
Neutrophil to Lymphocyte Ratio	73.7%	68.9%	68.9%	73.7%	71.2%

## DISCUSSION

This study was conducted to determine the usefulness of the neutrophil-to-lymphocyte ratio in determining whether acute cholecystitis was present in a patient in whom the disease was clinically suspected. The majority of patients suffering from acute cholecystitis were female in our study, i.e., 81(68.6%) patients, which is consistent with existing data suggesting that the disease is two to three-fold more common in women than in men.<sup>12,13</sup> Our sample demonstrated a high mean body mass index of  $29.12 \pm 2.68 \text{ kg/m}^2$ , which is also consistent with existing knowledge.<sup>14,15</sup> proposing that a higher body mass index translates into a higher risk for the development of cholesterol gallstones, a fact which is validated by studies like Rincon *et al.* who studied demographics and physical factors of patients suffering from acute cholecystitis and found that these patients had a mean body mass index of  $26.7 \pm 4.9 \text{ kg/m}^2$ .<sup>16</sup>

Our study showed that total leucocyte count in the presence of clinical signs of acute cholecystitis with a cut-off level of  $11.0 \times 10^9/\mu\text{L}$  carries a sensitivity of 67.1%, specificity of 73.3%, positive predictive value of 80.3% and a negative predictive value and diagnostic accuracy of 57.9% and 69.5%, respectively. That was similar to previous studies such as Beliaev *et al.* who reported a sensitivity of 73.0%, a specificity of 76.0% and a diagnostic accuracy of 74.0%, and reported that total leucocyte counts alone were insufficient in establishing or negating a diagnosis of acute cholecystitis.<sup>17</sup>

Our study aimed to establish whether the neutrophil-to-lymphocyte ratio would have better accuracy than the total leucocyte counts in predicting the presence of acute cholecystitis. However, our study showed that this was not the case, with the aforementioned ratio having similar values to total leucocyte count: with a sensitivity of 73.7%, a specificity of 68.9%, a positive predictive value of 68.9%, and a negative predictive value and diagnostic accuracy of 73.7% and 71.2%, respectively. At this juncture, it must be noted that our study found that females tended to have higher total leucocyte counts and higher neutrophil-to-lymphocyte ratios on presentation. We attribute this difference between genders to the late presentation of women to healthcare in general in Pakistan, which is attributed to a wide variety of reasons.<sup>18</sup> A study by Mahmood *et al.* reported a sensitivity of 71.7% and a specificity of 66.9% despite using higher cut-off values in detecting severity.<sup>19</sup>

Conversely, Aftab *et al.* reported that neutrophil to lymphocyte ratio had better discerning ability in their study, with a sensitivity of 79.3%, a specificity of 78.3%, and a diagnostic accuracy of 78.8%, higher than our study.<sup>20</sup> Micić *et al.* reported better results in their study with neutrophil to lymphocyte ratio showing a sensitivity of 78.3% and a specificity of 74.3%.<sup>21</sup> While Ay *et al.* reported a high sensitivity of 77.5% but a low specificity of 67.5%, values.<sup>22</sup> We believe that the difference in results here is because of the different cut-off values used to signify the presence of acute cholecystitis in these studies. In addition, Aftab *et al.* and Micić *et al.* only considered cases where severe acute cholecystitis was suspected, which may have increased the discriminating power of the test.

Overall, the neutrophil to lymphocyte ratio has comparable diagnostic accuracy to raised leucocyte counts in detecting the presence of acute cholecystitis and offers no real advantage over the latter test.

## LIMITATIONS OF STUDY

This study was limited by its sample size and the fact that it was being carried out in a single centre. Moreover, findings on contrast-enhanced computed tomography abdomen were operator-dependent, and while the reviewers were fully qualified, this may have produced some degree of bias in the results. Moreover, the study did not cater for patients with acute-on-chronic cholecystitis, which may cause disturbances in the neutrophil-to-lymphocyte ratio.

## CONCLUSION

The neutrophil to lymphocyte ratio is a readily available modality to determine whether acute inflammation is present or not and can be readily calculated in patients

with acute cholecystitis, with no added cost, as most, if not all, patients undergo complete blood counts as a routine. However, the test does not have the diagnostic accuracy to be used in isolation to diagnose acute cholecystitis in conjunction with clinical signs only, nor does it offer a significant benefit over raised total leucocyte counts in terms of diagnostic accuracy.

### ACKNOWLEDGEMENT

We want to express our deep gratitude to Dr Usman Bin Ali and Dr Neelofur Saeed. We would also like to thank the Pathology and Radiology Departments of Combined Military Hospital Rawalpindi for their help in offering us the resources to run this research study.

**Conflict of Interest:** None.

### Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

**MUK & MAA:** Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

**AZ & ZUR:** Data acquisition, critical review, approval of the final version to be published.

**MS & FF:** Concept, study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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