Cross-sectional Study

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Utility of perioperative ultrasonography and fine-needle aspiration cytology in differentiation between benign and malignant cervical lymphadenopathy: a retrospective cohort study

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Background: The preoperative differentiation of benign form malignant cervical lymphadenopathy (CLA) is crucial in determining the need for surgical intervention. This study aims to assess the diagnostic performance of ultrasonography (US), fine-needle aspiration cytology (FNAC), and their combination with the postoperative histopathological diagnoses of CLA.

Method: In a retrospective study between April 2021 and May 2023, 214 patients with CLA were assessed with preoperative US and FNAC. The morphological parameters, including tissue margins, vascularity, and fatty hilum echogenicity, were collected and analyzed retrospectively. The diagnostic efficacies of US, FNAC, and their combined use were compared to the postoperative histopathological findings.

Result: In the final histopathological examination, 185 cases (86.4%) were found to be benign, while 29 cases (13.6%) were determined to be malignant. The US features of fatty hilum, echogenicity, and vascularity pattern had the highest diagnostic accuracy in characterizing CLA patterns, with values of 88.3%, 85.5%, and 85.0%, respectively. The receiver operating characteristic (ROC) curve showed a significantly higher area under the curve (AUC) value of 0.883 (95% CI: 0.832–0.923; $P < 0.0001$) for the combined use of all US parameters with better sensitivity (93.10%) and specificity (68.65%) than individual parameters. The overall sensitivity, specificity, and accuracy of FNAC were 97.3%, 82.8%, and 95.3%, respectively. Additionally, US parameters and FNAC together showed a significantly higher AUC value of 0.924 (95% CI: 0.880–0.956; $P < 0.0001$) and achieved a sensitivity of 86.21% and specificity of 88.65%.

Conclusions: The combined use of US and FNAC provides high sensitivity, specificity, and diagnostic accuracy in characterizing CLA patterns. In limited-resources settings, this approach is feasible, less invasive, and cost-effective, thereby enabling clear management strategies and avoiding additional surgical interventions.

Keywords: cervical lymph nodes, fine-needle aspiration cytology, histopathological examination, ultrasound

Introduction

Lymphadenopathy refers to the alteration in lymph nodes' consistency, number, or size. In the cervical region, a lymph node diameter greater than 1 cm is commonly used to define cervical lymphadenopathy (CLA)[1]. Multiple processes can lead to CLA; however, it is generally classified as either hyperplastic, secondary to infectious or immunologic responses, or infiltrative, which may include various benign and malignant neoplasms[1]. While clinical examination can be valuable in the initial evaluation of lymphadenopathy, it has limited sensitivity and specificity. In addition, it poorly differentiates benign from malignant lesions[2]. The cervical region has a complex anatomy, with a dense lymphatic network receiving drainage from naso-oropharyngeal structures in addition to the upper airways[3]. Furthermore, the presence of extensive vasculature renders the cervical region

HIGHLIGHTS

- Cervical lymphadenopathy (CLA) can be inflammatory or neoplastic.
- Diagnosis of benign/malignant CLA is crucial in determining surgical need.
- Combined ultrasonography (USG) and fine-needle aspiration cytology (FNAC) provide high accuracy in characterizing CLA patterns.
- In limited-resources settings, this approach is feasible and cost-effective.

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vulnerable to vascular injury with subsequent vascular compromise[4].

As the development of CLA can be attributed to various factors, ranging from localized infection (e.g. adenovirus) to malignant metastasis or primary haematological proliferation, the need for further diagnostic evaluation is necessary for suspicious CLA cases[5]. However, the risk of complications should be minimized. The American Academy of Otolaryngology-Head and Neck Surgery has emphasized the importance of careful consideration when utilizing core biopsy, particularly due to the risks it poses to patients who may have benign lesions[6,7]. Ultrasonography (US) and fine-needle aspiration cytology (FNAC) have been utilized for the evaluation of CLA, both of which are readily available, feasible, and reproducible[8]. Nevertheless, the use of the US has been predominantly confined to serving as an adjunct for FNAC guidance[9]. Moreover, the use of US has been shown to provide significant diagnostic value in CLA cases, particularly when incorporated with Doppler US[10]. This approach can be beneficial in limited resources, where financial constraints and patient follow-up challenges can limit the quality of healthcare delivery[11]. The diagnostic value of preoperative FNAC and US features, separately and combined, in comparison with postoperative histopathological examination findings in patients with CLA were examined in prior studies with variable outcomes. Nevertheless, the applicability of such approach in resource-constrained settings is limited. This study aimed to investigate the diagnostic value of preoperative FNAC and US features, separately and combined, in comparison with postoperative histopathological examination findings in patients with CLA in resource-limited settings.

Material and methods

Study design and settings

This is a retrospective cohort study, that included 214 patients who were managed at Ibb University-affiliated hospitals. All patients with cystic lateral neck lump (More than 10 mm) with no evidence of primary tumour who underwent cervical lymph node excisional biopsy between April 2021 and May 2023 were included. The study excluded patients without preoperative US or FNAC evaluations or documentation, as well as those with infectious etiologies, evidence of a primary tumour at clinical examination with endoscopy, past head and neck oncological surgery, neoadjuvant radiotherapy, solid aspect of the neck mass, and patients who did not undergo excisional biopsy.

Ethical approval for the study was obtained from the ethics committees, and we conducted the study in accordance with the Helsinki Declaration. The manuscript has been reported in line with the STROCSS criteria[12].

Data collection

A detailed and precise history, including age, sex, laterality, and duration of symptoms, was carried out. Comprehensive clinical examination findings of the lymph node for site, size, laterality, number, mobility, uniformity, tenderness, extent of cervical lymph node, and systemic inspection were carried out.

US findings

The ultrasonographic evaluation of lymph nodes included an assessment of their size, number, and location. In addition, morphological analysis was performed, which included measuring the short-axis dimension (threshold of 11 mm), short-to-long axis (S/L) ratio (cut-off value of 0.6), fatty hilum presence, echogenicity (homogenous or heterogeneous), calcification, and lymph node margins regularity. The vascularity of the lymph nodes was also evaluated using colour Doppler imaging (CDI), and categorized into three distinct patterns: pattern 1, indicative of hilar vascularity or no flow, suggesting benign characteristics; pattern 2, representing peripheral vascularity; and pattern 3, denoting mixed vascularity, both of which were considered indicative of malignant characteristics[10,13]. Features suggestive of malignancy included an L/S ratio greater than 0.6, short-axis dimension greater than 11, indistinct boundaries, hypoechoic nature, heterogeneous echogenicity, absence of lymphatic hilum, and abnormal blood flow patterns.

FNAC findings

To consider the FNAC sample adequate, it should be obtained using a 22-gauge needle connected to a 10 ml syringe. Furthermore, the sample must include both the cortical and subcapsular regions of the lymph node.

Main outcome

Investigate the diagnostic value of FNAC and US findings in comparison with postoperative histopathological diagnoses of cervical lymph node excisional biopsy (Fig. 1).

The cytological examination results were categorized into six distinct groups: chronic granulomatous lymphadenitis, reactive lymphadenitis, acute inflammatory lesion, abscess, chronic lymphadenitis, and suspected malignant lesion. For ease of incorporation into diagnostic performance analysis, these outcomes were further classified on a binary scale. This scale differentiated between benign lesions (including chronic granulomatous lymphadenitis, reactive lymphadenitis, acute inflammatory lesion, abscess, and chronic lymphadenitis) and malignant lesions (encompassing lymphoma, malignancy, and suspected malignancy).

Statistical analysis

IBM SPSS software, version 22 (IBM Corp.) was used for statistical analysis. For quantitative data, means and standard deviations were utilized for description, whereas qualitative data were presented using frequencies and percentages. The sensitivity with 95% CI, specificity with 95% CI, positive predictive value (PPV), negative predictive value (NPV), overall accuracy, and the rate of discordance were calculated. The sensitivity was calculated as the ability of US and FNAC to detect malignant lesions, while specificity calculations used the benign cases. The χ^2 test was employed for comparing categorical variables across different groups. For continuous variables, the analysis involved using the Student's *t*-test and Fisher's exact test. A *P* value of less than 0.05 was considered statistically significant. Furthermore, a receiver operating characteristic (ROC) curve was created to assess the diagnostic efficacy of US features alone, and in combination with FNAC, for predicting malignancy. A ROC curve was constructed to determine the most optimal measurable cut-off for diagnosis[10,13,14].

Figure 1. Showing the preoperative cystic lateral neck mass (A, B) and the surgical removal (C, D).

Results

A total of 214 patients with CLA underwent cervical lymph node excisional biopsy. Of these, benign lymph nodes were 185 (86.4%) and malignant lymph nodes were 29 (13.6%). Demographic characteristics of patients are explained in detail in Table 1. The mean age in our study was 27.3 ± 17.2 years (range 2–80 years). The commonest age group was 10-20 years ($n = 56$; 26.2%), followed by 20–30 years ($n = 44$, 20.6%). There were 112 (52.3%) male and 102 (47.7%) female patients. The mean duration of symptoms was 4.6 ± 3.4 months (range 0.5–15 months). Most of the lymph node was located on the right side 97 (45.3%). The main symptoms were fever (36.9%), sweating (30.4%), and weight loss (20.1%). Splenomegaly was seen in (7.0%) of cases, while CLA presentation on the other side was seen in 23 (10.7%) cases.

Fine-needle aspiration cytology

Most of the reported benign FNAC cases 180 (97.3%)/185 were accurately accomplished with final histopathological reports. 24 (82.8%)/ 29 malignant cases were accurately reported in FNAC. However, 5 (2.7%) of malignant lesions were reported as benign lesions. Regarding false positive cases, 3.0 (10.3%) cases of reactive lymphadenitis, 1.0 (3.4%) cases of granulomatous lymphadenitis, and 2.0 (6.9%) cases of acute suppurative lymphadenitis were reported as malignant cases in final needle aspiration biopsy result. The overall sensitivity, specificity, PPV, NPV, and accuracy were 97.3% (95% CI: 93.8–99.1%), 82.8% (95% CI: 64.2–94.2%), 97.3%, 82.8%, and 95.3%, respectively. The reported benign and malignant cases in FNAC were statistically significant between groups ($P < 0.001$). Reactive lymphadenitis and granulomatous lymphadenitis constituted the majority of benign CLA cases, accounting for 86.0 (40.2%) and 66 (30.8%) of the cases, respectively (Fig. 2). On the other hand, metastasis accounted for the majority (78%) of malignant CLA cases, primarily from squamous cell carcinoma of the head and neck region

Table 1

Patient characteristics

Variables	*N* (%)
Age (year), Mean ± SD	27.3 ± 17.2 (range 2.0–80.0)
Sex	
Male	112 (52.3)
Female	102 (47.7)
Duration (months), Mean ± SD	4.6 ± 3.4 (range 0.5–15.0)
Side	
Right	97 (45.3)
Left	78 (36.4)
Bilateral	39 (18.2)
Symptoms	
Fever	79 (36.9)
Sweating	65 (30.4)
Weight loss	43 (20.1)
Splenomegaly	15 (7.0)
Lymphadenopathy on the other side	23 (10.7)
Histopathology result	
Benign	185 (86.4)
Malignant	29 (13.6)

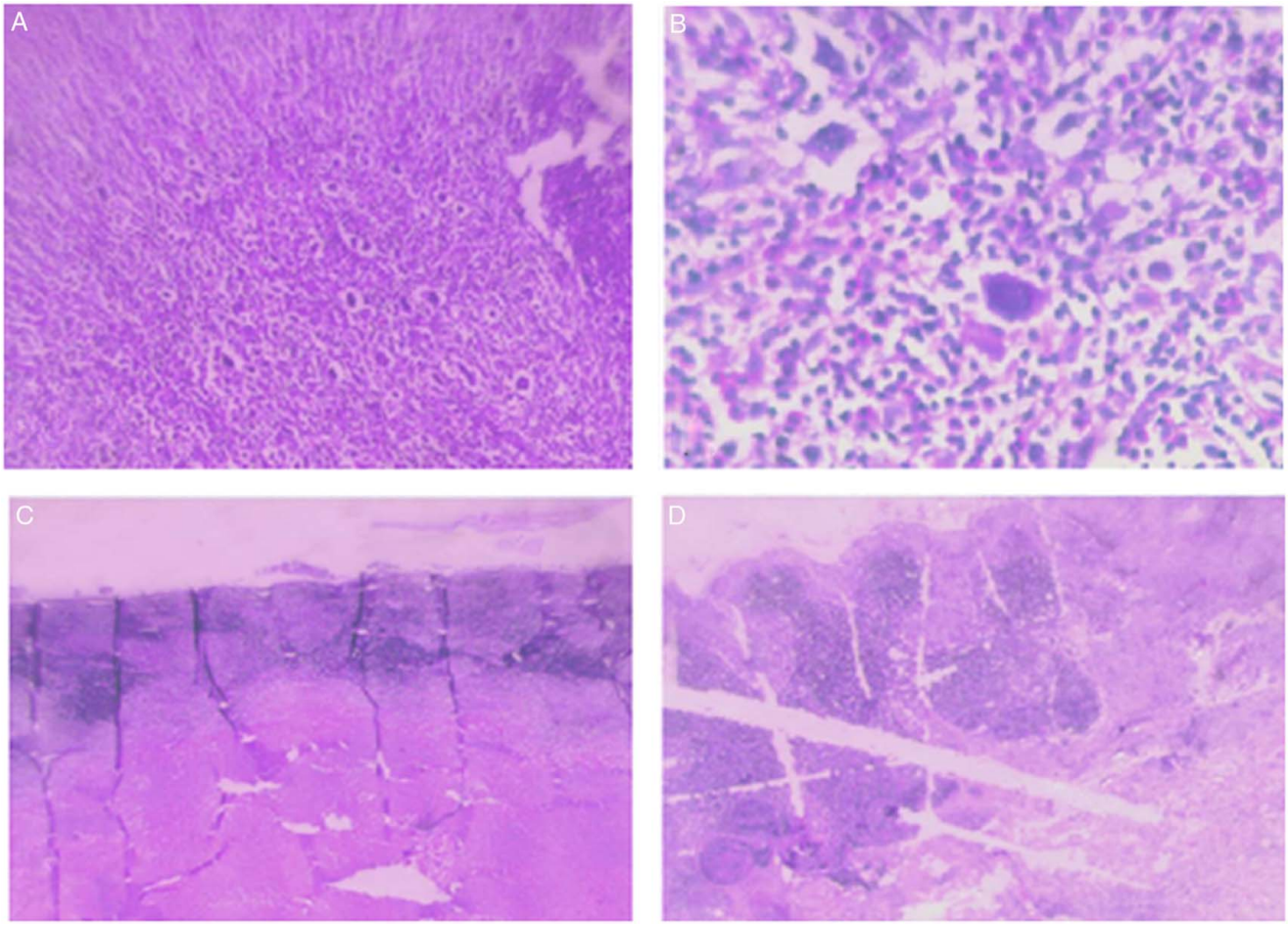

Figure 2. Histopathological images showing: (A) lacunar variant of RS cells suggestive of classic Hodgkin lymphoma (nodular sclerosis subtype). (B) classic Hodgkin lymphoma (magnification 40×), (C) Tuberculous lymphadenitis, (D) reactive lymphadenitis.

14 (48.2%), lymphoma in 10 (34.5%), and adenocarcinoma in 5 (17.3%). Whereas lymphoma cases accounted for 22% of malignant CLA cases (Table 2).

Ultrasonography findings

The ultrasonography findings are summarized in Table 3.

Lymph node margin

Regular margins were observed in 64.3% of benign CLA cases. Among the 29 malignant cervical nodes, 14 (48.3%) exhibited regular margins, while 15 (51.7%) displayed irregular margins. The sensitivity, specificity, PPV, NPV, and accuracy rates were 64.3% (95% CI: 57.0–71.2%), 51.7% (95% CI: 32.5–70.6%), 89.5%, 18.5%, and 62.6%, respectively, with no statistical significance noted ($P = 0.104$).

Lymph node echogenicity

The echogenicity was homogenous in 169 (91.4%) of benign CLA cases. On the other hand, malignant CLA showed homogenous and heterogenous echotexture in 15 (51.7%) and 14 (48.3%) of the cases, respectively. The sensitivity, specificity, PPV, NPV, and accuracy were 91.4% (95% CI: 86.3–95.0%), 48.3% (95% CI: 29.4–67.5%), 91.8%, 46.7%, and 85.5%, respectively, with statistical significance noted ($P < 0.001$).

Fatty hilum

A preserved fatty hilum was seen in most benign cases 173 (93.5%). While 16 (55.2%) of malignant cases showed the absence of fatty hilum. The sensitivity, specificity, PPV, NPV, and accuracy were 93.5% (95% CI: 88.9–96.6%), 55.2% (95% CI: 35.7–73.6%), 93.0%, 57.1%, and 88.3%, respectively, with statistical significance noted ($P < 0.001$).

Vascularity on colour doppler imaging

Pattern 1 (hilar vascularity or no flow) was observed in 165 (89.2%) and 12 (41.4%) of benign and malignant CLA, respectively. Either pattern 2 (peripheral) or pattern 3 (mixed vascularity) were observed in 17 (58.6%) of malignant CLA, and only in 20 (10.8) of benign cases. The sensitivity, specificity, PPV, NPV, and accuracy were 89.2% (95% CI: 83.8–93.3%), 58.6% (95% CI: 38.9–76.5%), 93.2%, 45.9%, and 85.0%, respectively, with statistical significance noted ($P < 0.001$) (Fig. 3).

Table 2

A comparison between final needle aspiration biopsy and surgical removal of lymph node pathological result

FNAC	Total ($N=214$)	Reactive lymphadenitis ($N=93$)	Granulomatous lymphadenitis ($N=70$)	Caseous necrotizing lymphadenitis ($N=12$)	Acute suppurative lymphadenitis ($N=10$)	Malignant ($N=29$)	*P*
Reactive lymphadenitis	86.0 (40.2)	83.0 (89.2)	0.0	0.0	0.0	3.0 (10.3)	< 0.001
Granulomatous lymphadenitis	66.0 (30.8)	2.0 (2.2)	61.0 (87.1)	2.0 (16.7)	0.0	1.0 (3.4)	
Caseous necrotizing lymphadenitis	23.0 (10.7)	4.0 (4.3)	9.0 (12.9)	10.0 (83.3)	0.0	0.0	
Acute suppurative lymphadenitis	12.0 (5.6)	0.0	0.0	0.0	10.0 (100.0)	2.0 (6.9)	
Malignant	27.0 (12.6)	4.0 (4.3)	0.0	0.0	0.0	23.0 (79.3)	

FNAC, fine-needle aspiration cytology.

Short/long-axis ratio (S/L ratio)

An S/L ratio of less than 0.6 was observed in 144 (77.8%) and 23 (79.3%) of benign and malignant CLA, respectively. The sensitivity, specificity, PPV, NPV, and accuracy were 77.8% (95% CI: 71.2–83.6%), 20.7% (95% CI: 8.0–39.7%), 86.2%, 12.8%, and 70.1%, respectively, with no statistical significance noted ($P=1.000$).

Short-axis dimension

Short-axis dimension of less than 11 was observed in 133 (71.9%) of benign CLA cases, while 29 (100.0%) of malignant CLA cases exhibited a large short-axis dimension (> 11 mm). The sensitivity, specificity, PPV, NPV, and accuracy were 71.9% (95% CI: 64.8–78.2%),100.0% (95% CI: 88.1–100.0%), 100.0%, 35.8%, and 75.7%, respectively, with statistical significance noted ($P<0.001$).

Correlation of US findings with histopathological findings

Fatty hilum, echogenicity, and vascularity pattern in the US demonstrated the highest diagnostic accuracy, correlating with histopathological findings at 88.3%, 85.5%, and 85.0%, respectively.

Correlation of combined US findings and FNAC with histopathological findings

Additionally, ROC curve analysis was performed, incorporating FNAC along with other quantitative US measures, namely short-axis dimension, short-to-long axis ratio, and lymph node margin regularity. This was done to evaluate their correlation with the findings from excisional biopsy histopathology. The combined use of these parameters yielded a significantly higher area under the curve (AUC) value of 0.883 (95% CI: 0.832–0.923; $P<0.0001$) in ROC curve analysis. This combination also resulted in higher sensitivity (93.10%) and specificity (68.65%) compared to the individual parameters (Fig. 4).

Table 3

Sensitivity, Specificity, positive predictive value, negative predictive value, and accuracy for ultrasonography parameters and final needle aspiration biopsy results.

Variables	Subgroups	Total	Benign	Malignant	Sensitivity	Specificity	PPV	NPV	Accuracy	*P*
Margin	Regular	133 (62.1)	119 (64.3)	14 (48.3)	64.3%	51.7%	89.5%	18.5%	62.6%	0.104
	Irregular	81 (37.9)	66 (35.7)	15 (51.7)						
Echogenicity	Homogenous	184 (86.0)	169 (91.4)	15 (51.7)	91.4%	48.3%	91.8%	46.7%	85.5%	**< 0.001**
	Heterogeneous	30 (14.0)	16 (8.6)	14 (48.3)						
Fatty hilum	Preserved	186 (86.9)	173 (93.5)	13 (44.8)	93.5%	55.2%	93.0%	57.1%	88.3%	**< 0.001**
	Absent	28 (13.1)	12 (6.5)	16 (55.2)						
Vascularity	Pattern 1	177 (82.7)	165 (89.2)	12 (41.4)	89.2%	58.6%	93.2%	45.9%	85.0%	**< 0.001**
	Pattern 2 or 3	37 (17.3)	20 (10.8)	17 (58.6)						
Short/long-axis ratio	< 0.6 mm	167 (78.0)	144 (77.8)	23 (79.3)	77.8%	20.7%	86.2%	12.8%	70.1%	1.000
	≥ 0.6 mm	47 (22.0)	41 (22.2)	6 (20.7)						
Short-axis dimension	< 11 mm	133 (62.1)	133 (71.9)	0 (0.0)	71.9%	100.0%	100.0%	35.8%	75.7%	**< 0.001**
	> 11 mm	81 (37.9)	52 (28.1)	29 (100.0)						
FNAC	Benign	185.0 (86.4%)	180.0 (97.3%)	5.0 (17.2%)	97.3%	82.8%	97.3%	82.8%	95.3%	**< 0.001**
	Malignant	29.0 (13.6%)	5.0 (2.7%)	24.0 (82.8%)						

Boldface indicates a statistically significant result ($P<0.05$).

FNAC, fine-needle aspiration cytology; NPV, negative predictive value; PPV, positive predictive value.

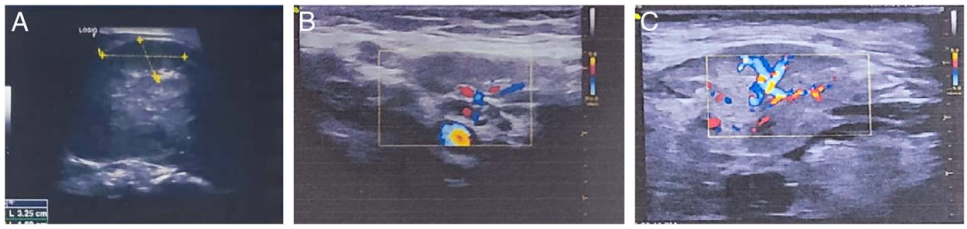

Figure 3. Ultrasonography image showing an oval-shaped lymph node still preserved fatty helium (A), hypervascular on colour Doppler hailer pattern (B); mixed pattern (C).

Correlation of combination of US features and FNAC with pathological diagnosis

US and FNAC together showed a significantly higher AUC value of 0.924 (95% CI: 0.880–0.956; $P < 0.0001$) and achieved a sensitivity of 86.21% and specificity of 88.65% (Fig. 5).

Discussion

The assessment of CLA presents a diagnostic challenge, primarily due to the limited information garnered from clinical evaluations alone. In addition, the diverse range of pathologies leading to CLA, coupled with the clinical imperative to exclude malignant processes, often necessitates reliance on more invasive diagnostic approaches, such as FNAC or excisional biopsies[15]. Our study aimed to evaluate the diagnostic accuracy of US findings and FNAC, both separately and in conjunction with FNAC, against the histopathological examination of removed lymph nodes, which is considered the gold standard in diagnostic testing. While advanced imaging techniques like computed tomography (CT) are often presumed to offer superior diagnostic accuracy, empirical evidence from retrospective analyses does not consistently demonstrate a significant diagnostic advantage of CT scans over US[16]. Furthermore, the utilization of CT scans is associated with increased radiation exposure and higher costs[17]. Consequently, it is judicious to consider the use of the US as a primary tool in the initial evaluation of CLA. While the US not only provides insights into the size, location, number, shape, and margins of the lymph nodes, the application of brightness modulation (B-mode) parameters and the utilization of CDI can enhance its diagnostic and predictive value[18].

In our analysis, margin irregularity was more commonly observed in malignant CLA cases; however, this difference was not statistically significant, aligning with previous observations[19,20]. We did not observe a statistically significant correlation of the Short/long-axis ratio, diverging from previously reported studies[13,21]. Nevertheless, a statistically significant association was noted in the short-axis diameter, echoing the findings of van den Brekel *et al.*[22] In our study, a short-axis

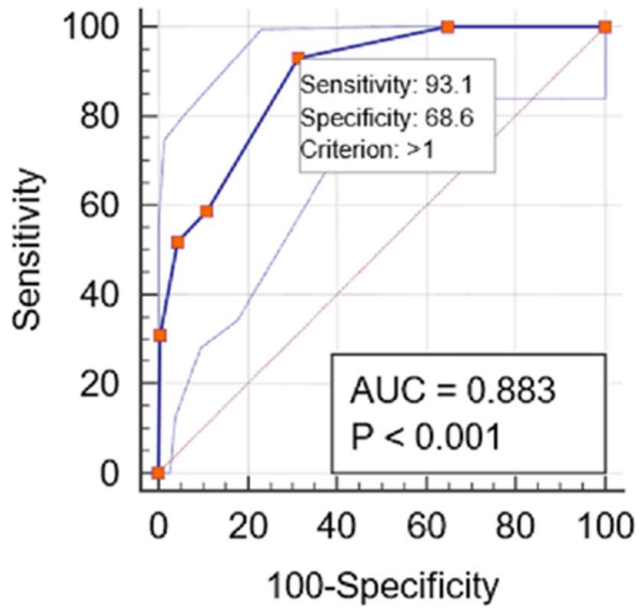

Figure 4. The receiver operating characteristic curve showed a significantly higher area under the curve (AUC) value of 0.883 (95% CI: 0.832–0.923; $P < 0.0001$) for the combined use of all ultrasonography parameters with better sensitivity (93.10%) and specificity (68.65%) than individual parameters.

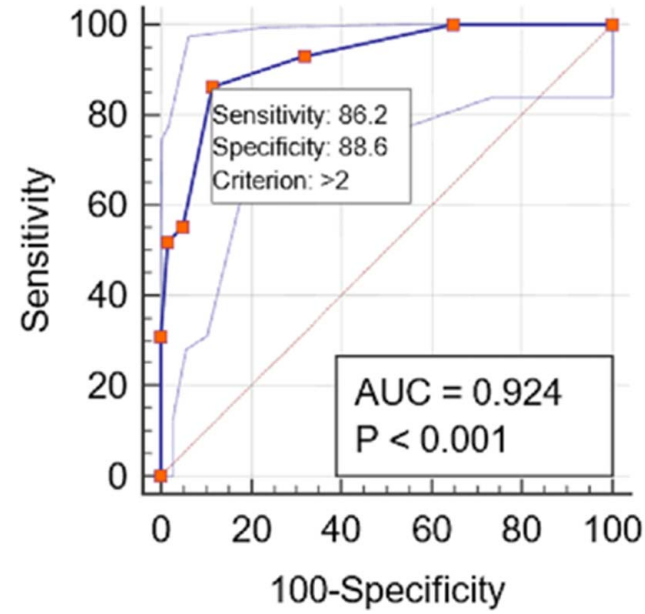

Figure 5. The receiver operating characteristic curve of combined ultrasonography features and fine-needle aspiration cytology showed a significantly higher area under the curve (AUC) value of 0.924 (95% CI: 0.880–0.956; $P < 0.0001$) and achieved a sensitivity of 86.21% and specificity of 88.65%.

dimension greater than 11 mm was associated with malignant CLA, yielding a sensitivity, specificity, PPV, NPV, and accuracy of 71.9%, 100.0%, 100.0%, 35.8%, and 75.7%, respectively. It is important to note that varying cut-offs have been used in different studies, depending on lymph node levels. For example, Alam *et al.*[23] achieved a diagnostic accuracy of 84% with variable cut-offs in Eighty-five lymph nodes (metastatic, $n = 53$; reactive, $n = 32$) from 37 patients. However, while using 11 mm as a cut-off demonstrates high specificity, it has limited sensitivity, increasing the risk of false-negative results.

Fatty hilum had the highest diagnostic accuracy in our study at 88.3%, with the loss of fatty hilum echogenicity being associated with malignant CLA, in line with prior research[21,24]. Despite the high sensitivity of hilar characteristics (93.5% in our study), the specificity was relatively low at 55.2%. Lymph node echogenicity represents another crucial parameter, with benign CLA lesions tending to be homogenous, compared to the heterogenicity noted in malignant CLA lesions. Our analysis showed a sensitivity, specificity, and accuracy of 91.4%, 48.3%, and 85.5%, respectively for lymph node echogenicity. The latter was relatively higher compared to the 67% (benign lymph nodes were 26 out of 84) reported by Abdelgawad *et al.*[14]

The vascularity pattern, utilizing US with CDI had a diagnostic accuracy of 85%, in our analysis, surpassing the 70% accuracy (benign lymph nodes were 46/ 78 and malignant lymph nodes were 32/ 78) reported by Vineela *et al.*[13] Generally, malignant CLA cases tended to exhibit either pattern 2 (peripheral) or pattern 3 (mixed vascularity), observed in 17 (58.6%) malignant CLA cases and only in 20 (10.8%) benign cases. These results are consistent with multiple studies, though they reported a lower diagnostic accuracy but higher specificity[25,26].

We further performed ROC curve analysis, integrating B-mode parameters such as fatty hilum characteristics, echogenicity, short-axis dimension, short-to-long axis ratio, and lymph node margin regularity, along with CDI vascularity findings, to correlate with excisional biopsy histopathology results. This combined approach yielded a significantly higher AUC value of 0.883 (95% CI: 0.832–0.923; $P < 0.0001$) in the ROC analysis, offering increased sensitivity (93.10%) and specificity (68.65%) compared to using these parameters individually. Vineela *et al.*[13] reported similar findings but with a higher specificity of 90%. Conversely, Moharram *et al.*[27] demonstrated a higher overall diagnostic accuracy with a specificity of 100%. In this study after revising cytological results out of 32/75 (42.6%) LNs diagnosed as benign by elastographic scoring 25/32 (76.9%) were proven cytological to be benign (true negative) and another 7/32 (23.1%) LNs were proven pathologically to be malignant (false negative) (five of them were confirmed to be lymphoma while the other two were metastasis from nasopharyngeal carcinoma). While after revising cytological results 43/75 (57.3%) were diagnosed as malignant by elastography scoring, and 43/43 (100%) LNs confirmed to be malignant by pathology (true positive). The lower specificity in our study might be due to the variability in parameters and cut-offs used in each study; for example, our study, akin to Vineela and colleagues, adopted a more inclusive approach to various US parameters. Pattanayak *et al.*[24] reported a specificity of 73%, which is closer to our findings. These results highlight the limitations of the US, including operator dependence and interobserver variability.

FNAC is a commonly used tool in evaluating CLA, valued for its minimally invasive nature and cost-effectiveness. In our study, the majority of benign CLA cases, 180 (97.3%), correlated accurately with final histopathological reports. Of the malignant cases, 24 (82.8%) were accurately reported in FNAC. However, 5 (2.7%) malignant lesions were misclassified as benign. The diagnostic accuracy of FNAC in our study was consistent with most literature findings at 95.3%[28,29]. Nevertheless, there is noticeable variability in FNAC's sensitivity and specificity in CLA. In our study, the sensitivity, specificity, PPV, and NPV of FNAC were 97.3%, 82.8%, 97.3%, and 82.8%, respectively. Al Qout *et al.*[30] reported FNAC sensitivity, specificity, PPV, and NPV as 93.3%, 100%, 100%, and 86.7%, respectively. A recent systematic review and meta-analysis found the FNAC sensitivity, specificity, accuracy, PPV, and NPV to be 89.6%, 96.5%, 93.1%, 96.2%, and 90.3%, respectively[31]. However, in a study by Nesreen and colleagues, the sensitivity, specificity, PPV, and NPV of FNAC were 90.9%, 67.2%, 82.6%, and 81.3%, respectively[32]. Similarly, Rakhshan and Rakhshan reported FNAC sensitivity, specificity, PPV, and NPV as 75.8%, 96.6%, 94%, and 85%, respectively[33]. The observed variability was attributed, in part, to the artifact and inadequate sampling[6]. This variation became more evident when stratifying FNAC performance based on the underlying pathology. For instance, FNAC demonstrated lower sensitivity and overall accuracy in diagnosing primary haematological and lymphoproliferative disorders[6]. Additionally, these outcomes could be influenced by the operator's experience, as evidenced by Jandu *et al.*[34], who reported improved sensitivity, specificity, and diagnostic accuracy of FNAC when conducted by experienced personnel.

In our study, we integrated the US along with FNAC to enhance diagnostic performance, applying ROC curve analysis. Remarkably, our analysis revealed a significantly higher AUC value of 0.924 (95% CI: 0.880–0.956; $P < 0.0001$), achieving a sensitivity of 86.21% and a specificity of 88.65% for the combined use of US and FNAC. Gupta *et al.*[10] reported similar outcomes with sensitivity and specificity of 95.4% and 92.3%, respectively, when FNAC was used alongside the US. An even higher sensitivity of 98% and specificity of 95% were reported by Baatenburg de Jong *et al.*[35] using the same combined approach.

Study limitations

This study has several limitations. The data were collected retrospectively, relying on chart reviews from patients' medical records. This approach is affected by the quality of documentation and is vulnerable to selection and misclassification biases. Additionally, the measures used, including US and FNAC, can be influenced by the operator's experience and interpretation skills. Another limitation is that false-negative cases, not discernible by this study design, could potentially compromise the accuracy of the effect estimate. Furthermore, these tests ideally require specific approaches that can influence the overall results. Moreover, there is a lack of consistency in parameter cut-offs in the literature, leading to limited reproducibility and increased heterogeneity in findings. Lastly, the study focused on differentiating benign from malignant CLA lesions without stratifying each group by disease, which may affect the precision of the findings

Conclusions

Incorporating B-mode US and CDI parameters with FNAC findings can provide the highest diagnostic accuracy in

differentiating benign from malignant CLA. This approach is particularly feasible in settings with limited resources due to its ease, minimally invasive nature, reproducibility, and cost-effectiveness thereby enabling clear management strategies and avoiding additional surgical interventions.

Ethical approval

Ethical approval for this study (Ethical Committee N° IBBUNI. AC.YEM. 2023.59) was provided by the Research Ethics Committees of Ibb University, Faculty of Medicine and Health Science, Ibb, Yemen on 03 February 2020.

Informed consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

Conceptualization, S.G.; methodology, S.G., and F.A.; software, S.A., F.A., M.B., and A.A.; validation, S.G., M.B., and A.A.; formal analysis, F.A., F.G., A.A., and M.B.; investigation, S.A., A.A., S.A., and F.A.; resources, S.G., and F.A.; data curation, M.B., and A.A.; writing—original draft preparation, F.A., S.G., M.B., A.A.; writing—review and editing, F.A., and S.G.; visualization, F.A.; supervision, S.G.; project administration, A.A. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: UMIN Clinical Trials Registry.
2. Unique Identifying number or registration ID: UMIN000053717.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://center6.umin.ac.jp/cgibin/ctr_e/ctr_view_reg.cgi?recptno=R000061300.

Guarantor

Saif Ghabisha and Faisal Ahmed.

Data availability statement

The data presented in this study are available on request from the corresponding authors. The data are not publicly available due to local policies.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by Ibb University Institutional Ethics Committee.

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