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Original article

Clinical factors predicting the need for biopsy in children with cervical lymphadenopathy

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Abstract

Background: Diagnosing lymphadenopathy in children can be challenging for clinicians, as it may represent a manifestation of various conditions, including granulomatous diseases and malignancies. The cervical region is frequently affected in cases of peripheral lymphadenopathy. While surgical biopsy can provide a definitive diagnosis, it is not always necessary.

Objectives: This study aimed to characterize pediatric patients with cervical lymphadenopathy who underwent surgical biopsy and to identify clinical factors associated with lymph nodes that require further management (LNFM), such as those with granulomatous or malignant features.

Methods: A retrospective review was conducted on 87 pediatric cases of cervical lymphadenopathy that underwent surgical biopsy. A descriptive analysis was performed. Receiver operating characteristic (ROC) analysis was used to identify the lymph node size most indicative of LNFM. Logistic regression analysis was conducted to determine independent predictors of LNFM, granulomatous lymph nodes, and malignant lymph nodes.

Results: Final diagnoses revealed 37 cases (42.5%) as non-LNFM, 36 cases (41.4%) as granulomatous, and 14 cases (16.1%) as malignant lymph nodes. ROC analysis identified 2 cm as the optimal lymph node size threshold for predicting LNFM, balancing sensitivity and specificity. Multivariate logistic regression revealed that submandibular location (odds ratio (OR), 11.9; 95% confidence intervals (CI), 2.5–55.4; $P = 0.002$) and abnormal chest x-ray findings (OR, 20.7; 95% CI, 2.1–201.5; $P = 0.009$) were independent predictors of LNFM. Subgroup analysis further showed that overlying skin redness (OSR) (OR, 8.0; 95% CI, 1.1–58.8; $P = 0.04$) and submandibular location (OR, 9.7; 95% CI, 1.3–72.1; $P = 0.027$) were significant predictors of granulomatous lymph nodes. No significant predictors were found for malignant lymph nodes.

Conclusion: Submandibular location and abnormal chest x-ray findings serve as key predictors of LNFM. Lymph nodes exceeding 2 cm in size are more likely to fall into the LNFM category. OSR and submandibular involvement suggest granulomatous pathology. Most supraclavicular nodes were classified as LNFM and were frequently malignant, underscoring the need for careful assessment of this area. These findings may support clinical decision-making prior to biopsy in cases of cervical lymphadenopathy.

Keywords: Cervical lymphadenopathy, children, granulomatous lymphadenitis, lymphoma, reactive lymphoid hyperplasia.

Lymphadenopathy frequently occurs in children and often presents a diagnostic challenge for clinicians.[1] Enlargement of lymph nodes can result from the proliferation of normal cells, as seen in reactive or infectious conditions; infiltration by abnormal cells, as in malignancies; or suppuration due to nodal tissue necrosis.[1] Among peripheral lymphadenopathy cases, the cervical region is the most commonly affected site.[2] The reported incidence of cervical lymphadenopathy in children ranges from 62.0% in those aged 3 weeks to 6 months, to 41.0% in children aged 2–5 years, and up to 90.0% in children aged 4–8 years old.[3] Although surgical biopsy can often yield a definitive diagnosis, it is not always required.[1]

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Hodgkin lymphoma and non-Hodgkin lymphoma represent the two most common malignant causes of lymphadenopathy.[1] The presence of metastatic lymph nodes from malignancies such as rhabdomyosarcoma, melanoma, or tumors of the thyroid or salivary glands should prompt efforts to locate the primary tumor.[1,2] Consequently, malignancy should be considered in the differential diagnosis of any significantly enlarged or persistent lymphadenopathy and frequently serves as a rationale for surgical biopsy.[1]

In developing countries, tuberculosis accounts for a substantial proportion (50.0%) of peripheral lymphadenopathy cases and is the most frequent cause of cervical lymphadenopathy (62.5%).[4] Chronic cervical lymphadenitis may result from infection with *Mycobacterium tuberculosis* or nontuberculous *Mycobacterium* species.[1, 2] Histological evidence of granulomatous inflammation is indicative of infection by either *Mycobacterium tuberculosis* or nontuberculous *Mycobacterium*.[2] For uncomplicated nontuberculous lymphadenitis, complete surgical excision remains the most effective treatment. In children treated with incision and drainage alone, an additional surgical intervention—typically excision—is often required.[2,5,6] Therefore, complete excision serves both diagnostic and therapeutic purposes in cases of nontuberculous lymphadenitis.

Currently, surgical biopsy—usually excisional, though sometimes incisional—represents the gold standard for diagnosing cervical lymphadenopathy in children. However, it has limitations due to its invasive nature, potential requirement for general anesthesia, and increased risks of infection, neurovascular complications, and bleeding.[1,7] When deciding which patients to refer for biopsy, clinicians must carefully balance avoiding unnecessary procedures with the need to promptly diagnose malignancy.[7] The aim of this study was to describe pediatric patients with cervical lymphadenopathy who underwent surgical biopsy and to identify clinical factors that may predict whether lymph nodes require further management (LNFM), including those with granulomatous or malignant pathology.

Materials and methods

This study received approval from the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University, Thailand (IRB no. 194/64). A retrospective review was conducted on patients aged 0–15 years who present with clinically diagnosed cervical lymphadenopathy and underwent surgical biopsy between January 2017 and December 2020. Clinically diagnosed cervical lymphadenopathy was defined as an enlarged lymph node persisting for at least 1 month, where, after thorough clinical evaluation and physical examination, the underlying cause remained unidentified.

Patient medical records were reviewed to collect the following information: age and gender, presenting signs and symptoms, lymph node size and duration, laterality, anatomical location, laboratory results, chest x-ray findings, and histopathological diagnosis. The duration of lymphadenopathy was categorized into two groups: subacute (< 6 weeks) and chronic (≥ 6 weeks). Lymph node location was classified as cervical, submandibular, supraclavicular, or others (including submental, preauricular, postauricular, and generalized lymphadenopathy). Abnormal chest x-ray findings were defined as the presence of hilar adenopathy, pulmonary infiltration, or pulmonary metastasis. Histopathologic outcomes were grouped into two categories: LNFM and non-LNFM. Granulomatous and malignant lymph nodes were classified as LNFM. Comparative analyses were performed for the following groups: non-LNFM vs. LNFM, non-granulomatous vs. granulomatous lymph nodes, and non-malignant vs. malignant lymph nodes.

Statistical analysis

Data were presented as mean and standard deviation (SD). To compare two independent groups, unpaired *t*-tests were applied for continuous variables, and chi-squared tests were used for categorical variables. Logistic regression analysis was performed to calculate odds ratios (OR), with 95% confidence intervals (CI) provided to indicate the precision of the OR estimates. Multivariate logistic regression models were employed to identify independent predictors of LNFM, granulomatous lymph nodes, and malignant lymph nodes. In addition, receiver operating characteristic (ROC) curves were analyzed to evaluate lymph node size as a predictor for LNFM. Statistical analyses were conducted using Stata version 11 for Windows. A two-sided $P < 0.05$ was considered statistically significant.

Results

A total of 87 cases were included for review between January 2017 and December 2020. The histopathological findings are summarized in **Table 1.** Based on the final diagnosis, 37 lesions (42.5%) were classified as non-LNFM, 36 lesions (41.4%) as granulomatous lymph nodes, and 14 (16.1%) lesions as malignant lymph nodes. In the non-LNFM group, reactive lymph nodes were the most common diagnosis (25.3%). Among the granulomatous group, the most frequent diagnosis was provisional nontuberculous mycobacterial lymphadenitis (19.5%). Pulmonary involvement was identified in 3 of the 15 cases diagnosed with tuberculous lymphadenitis. Mycobacterial culture confirmed two cases of *Mycobacterium haemophilum* lymphadenitis, one case of *Mycobacterium intracellulare* lymphadenitis, and one case of *Mycobacterium fortuitum* lymphadenitis. In the malignant group, the most common diagnoses were lymphoma (4.6%) and post-transplant lymphoproliferative disorder (PTLD) (4.6%). All four patients with PTLD had a history of biliary atresia and had undergone living donor liver transplantation.

The clinical characteristics of patients—including gender, age, presenting signs and symptoms, lymph node size and duration, laterality, location, laboratory results, and chest x-ray findings—were compared between the non-LNFM and LNFM groups (**Table 2**), between non-granulomatous and granulomatous groups (**Table 3**), and between non-malignant and malignant lymph node groups (**Table 4**).

Table 1. Distribution of histopathologic outcomes in 87 cases with unexplained cervical lymphadenopathy.

Diagnosis	N	(%)
Benign lymph node	**37**	**42.5**
Reactive lymph node	23	26.4
Fibroadipose tissue	4	4.6
Kikuchi-Fujimoto disease	3	3.5
Pilomatricoma	2	2.3
Histiocytic lymph node	2	2.3
Fragment of spindle cells, mature fat and nerve	1	1.2
Organizing inflammation	1	1.2
Hematoma	1	1.2
Granulomatous lymph node	**36**	**41.4**
Provisional non-tuberculous mycobacterium Lymphadenitis	17	19.5
Tuberculous lymphadenitis	15	17.2
Mycobacterium Haemophilum lymphadenitis	2	2.3
Mycobacterium Intracellulare lymphadenitis	1	1.2
Mycobacterium Fortuitum lymphadenitis	1	1.2
Malignant lymph node	**14**	**16.1**
Lymphoma	4	4.6
Post-transplant lymphoproliferative disorder (PTLD)	4	4.6
Neuroblastoma	3	3.5
Adenocarcinoma of lung	1	1.2
Rhabdoid tumor	1	1.2
Spindle cell tumor	1	1.2
Total	**87**	**100.0**

Table 2. Clinical characteristics of lymphadenopathy in the non-LNFM and LNFM groups.

	N	Non-LNFM frequency (%) or mean (SD)	LNFM frequency (%) or mean (SD)	*P*-value
Age (years)	87	6.5 (4.4)	5.5 (4.6)	0.304
Gender	87			0.891
Male		22/37 (59.5%)	29/50 (58.0%)	
Female		15/37 (40.5%)	21/50 (42.0%)	
Duration	84			0.408
Subacute		19/35 (54.3%)	31/49 (63.3%)	
Chronic		16/35 (45.7%)	18/49 (36.7%)	
Side	87			0.583
Left		16/37 (43.2%)	16/50 (32.0%)	
Right		19/37 (51.4%)	29/50 (58.0%)	
Middle		0/37 (0.0%)	2/50 (4.0%)	
Bilateral		2/37 (5.4%)	3/50 (6.0%)	
*Overlying skin redness (OSR)	47	2/18 (11.1%)	12/29 (41.4%)	0.027
Pain	50	5/19 (26.3%)	11/31 (35.5%)	0.500
Fever	70	7/27 (25.9%)	11/43 (25.6%)	0.974
Chronic cough	14	0/6 (0.0%)	3/8 (37.5%)	0.209
Weight loss	45	2/18 (11.1%)	3/27 (11.1%)	1.000
*URI symptoms	53	3/22 (13.6%)	12/31 (38.7%)	0.046
*Increased size when followed up	69	7/29 (29.1%)	19/40 (47.5%)	0.048
Tuberculosis contact	57	3/19 (15.8%)	5/38 (13.2%)	1.000
*Size (cm) [median, IQR]	87	1.5 (0.5)	2 (1.5)	0.003
*Location	87			0.000
Cervical		26/37 (70.3%)	11/50 (22.0%)	
Submandibular		5/37 (13.5%)	18/50 (36.0%)	
Supraclavicular		1/37 (2.7%)	13/50 (26.0%)	
Others		5/37 (13.5%)	8/50 (16.0%)	
Consistency	65			0.463
Soft		5/26 (19.2%)	4/39 (10.3%)	
Firm		9/26 (34.6%)	18/39 (46.2%)	
Rubbery		11/26 (42.3%)	13/39 (33.3%)	
Hard		1/26 (3.9%)	4/39 (10.3%)	
*Fixed lymph node	56	2/28 (7.1%)	9/28 (32.1%)	0.019
Tenderness	70	8/31 (25.8%)	15/39 (38.5%)	0.263
*Abnormal CXR	51	1/24 (4.2%)	19/27 (41.3%)	0.001
*PPD skin test positive	43	2/14 (14.3%)	16/29 (55.2%)	0.011
Hemoglobin (g/dL)	49	11.7 (1.9)	11.1 (1.8)	0.339
Hematocrit (%)	49	35.4 (5.7)	34.3 (4.9)	0.459
Platelet count (cell/mm^3)	49	32,3055.6 (10,3380.8)	36,7290.3 (11,1404.4)	0.176
WBC (cell/mm^3)	49	8,510.0 (3,860.5)	10,402.3 (5,075.5)	0.178
Neutrophil count (%)	49	45.1 (17.0)	53.8 (16.1)	0.081
Absolute neutrophil count (cell/mm^3)	49	3,840.0 (2,154.4)	5,589.0 (3,680.0)	0.073
Lymphocyte count (%)	49	45.4 (16.8)	36.9 (16.3)	0.088
Absolute lymphocyte count (cell/mm^3)	49	3,926.1 (2,667.9)	3,846.5 (2,524.7)	0.917

Comparisons between non-LNFM and LNFM groups

Table 2 presents a comparison of clinical characteristics between the non-LNFM and LNFM groups. Statistically significant differences were observed between the two groups in relation to overlying skin redness (OSR), presence of upper respiratory infection (URI) symptoms, increase in lymph node size during follow-up, lymph node size, location, fixation of the lymph node, positive purified protein derivative (PPD) skin test, and abnormal chest x-ray findings. The median lymph node size (with interquartile range [IQR]) was 1.5 (0.5) cm in the non-LNFM group and 2 (1.5) cm in the LNFM group. The mean lymph node size was 1.8 ± 1.0 cm for non-LNFM and 2.7 ± 1.9 cm for LNFM. Within the LNFM group, the submandibular region was the most frequently affected site (36.0%), followed by the supraclavicular region (26.0%). In contrast, only one patient in the non-LNFM group had supraclavicular lymphadenopathy; this case was ultimately diagnosed as Kikuchi-Fujimoto disease.

A logistic regression model for predicting LNFM was developed using three variables. Descriptive statistics for these variables are summarized in **Table 3**. Univariate analysis revealed that LNFM was significantly associated with lymph node size (OR, 1.7; 95% CI, 1.1–2.6; $P = 0.013$), submandibular location (OR, 8.5; 95% CI, 2.5–28.7; $P = 0.001$), supraclavicular location (OR, 30.7; 95% CI, 3.6–264.5; $P = 0.002$), other locations (OR, 3.8; 95% CI, 1.0–14.2; $P = 0.048$), and abnormal chest x-ray (OR, 16.2; 95% CI, 2.0–130.4; $P = 0.009$). The ROC curve analysis for lymph node size in predicting LNFM (**Figure 1**) identified 2 cm as the size threshold that optimized sensitivity and specificity. Using a cutoff of ≥ 2 cm to classify LNFM yielded a sensitivity of 70.0% and specificity of 67.6%. The multivariate logistic regression model demonstrated that submandibular location (OR, 11.9; 95% CI, 2.5–55.4; $P = 0.002$) and abnormal chest x-ray (OR, 20.7; 95% CI, 2.1–201.5; $P = 0.009$) were significant independent predictors of LNFM.

Comparisons between non-granulomatous and granulomatous lymph node groups

Table 4 compares the clinical characteristics of patients between the non-granulomatous and granulomatous lymph node groups. Significant differences were found between these groups for OSR, fever, lymph node location, and positive PPD skin test. Within the granulomatous lymph node group, the submandibular area was the most commonly affected site (50.0%).

A logistic regression model to predict granulomatous lymph nodes was created using three variables. Descriptive statistics for these three variables are provided in **Table 5**. Univariate analysis showed associations between granulomatous lymph nodes and overlying redness (OSR, 13.8; 95% CI, 2.6–73.4; $P = 0.002$), fever (OR, 0.3; 95% CI, 0.08–0.91; $P = 0.035$), submandibular location (OR, 15.4; 95% CI, 4.3–55.9; $P < 0.000$), and other locations (OR, 5.0; 95% CI, 1.3–19.6; $P = 0.021$). In the multivariate logistic regression model, OR, 8.0; 95% CI, 1.1–58.8; $P = 0.040$) and submandibular location (OR, 9.7; 95% CI, 1.3–72.1; $P = 0.027$) remained significant independent predictors of granulomatous lymph nodes.

Table 3. Odds ratio for predictive factors for LNFM from univariate and multivariate logistic regression models.

	Univariate analysis		Multivariate analysis	
	Crude odds ratio (95% CI)	***P*-value**	**Adjusted odds ratio (95% CI)**	***P*-value**
Size (cm)	1.7 (1.1–2.6)	0.013	1.6 (1.0–2.5)	0.068
Location				
Cervical	Reference		Reference	
Submandibular	8.5 (2.5–28.7)	0.001	11.9 (2.5–55.4)	0.002
Supraclavicular	30.7 (3.6–264.5)	0.002	5.7 (0.4–80.6)	0.195
Others	3.8 (1.0–14.2)	0.048	3.0 (0.5–16.5)	0.208
Abnormal CXR	16.2 (2.0–130.4)	0.009	20.7 (2.1–201.5)	0.009

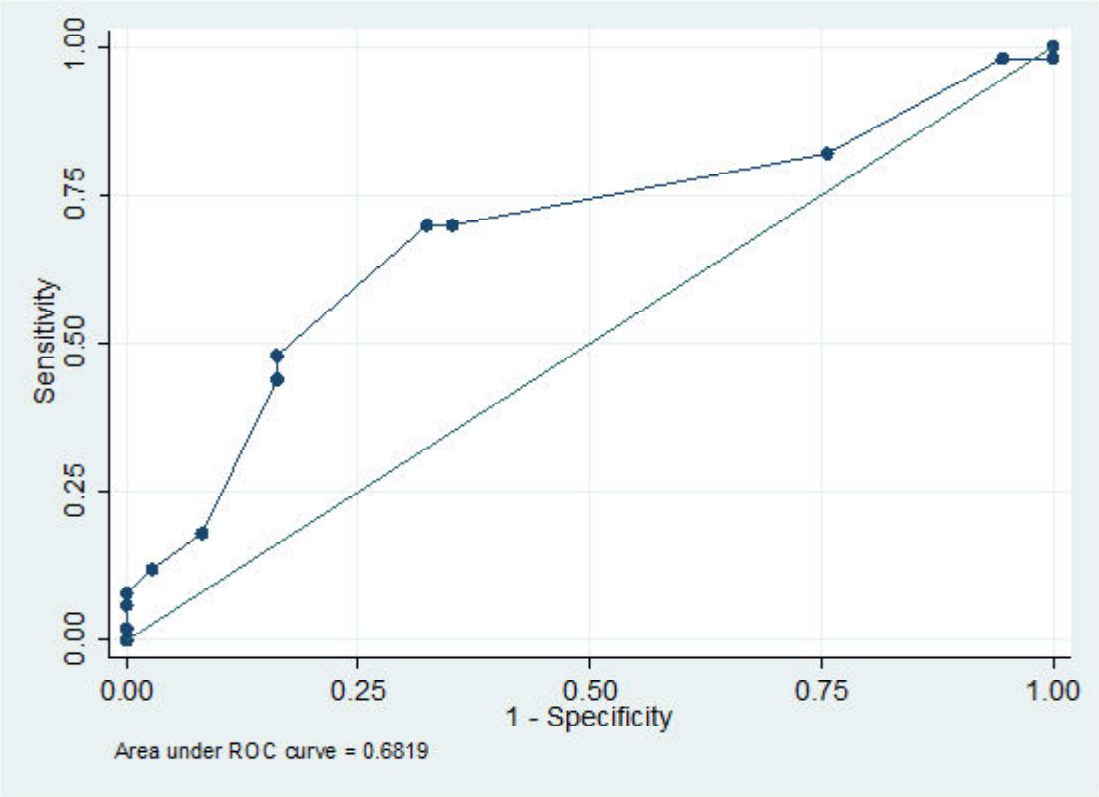

Figure 1. Receiver operating characteristics curves (ROC) of size (2 cm) for prediction of LNFM.

Table 4. Clinical characteristics of lymphadenopathy in the non-granulomatous and granulomatous lymph nodes group.

		Non-granulomatous lymph node	Granulomatous lymph node	*P*-value
	N	Frequency (%) or mean (SD)	Frequency (%) or mean (SD)	
Age (years)	87	6.5 (4.7)	5.1 (4.2)	0.145
Gender	87			0.964
Male		30/51 (58.8%)	21/36 (58.3%)	
Female		21/51 (41.2%)	15/36 (41.7%)	
Duration	84			0.521
Subacute		30/48 (62.5%)	20/36 (55.6%)	
Chronic		18/48 (37.5%)	16/36 (44.4%)	
Side	87			0.083
Left		23/51 (45.1%)	9/36 (25.0%)	
Right		26/51 (51.0%)	22/36 (61.1%)	
Middle		0/51 (0.0%)	2/36 (5.6%)	
Bilateral		2/51 (3.9%)	3/36 (8.3%)	
Overlying skin redness (OSR)	47	2/25 (8.0%)	12/22 (54.6%)	< 0.001*
Pain	50	6/26 (23.1%)	10/24 (41.7%)	0.159
Fever	70	14/39 (35.9%)	4/31 (12.9%)	0.029*
Chronic cough	14	2/9 (22.2%)	1/5 (20.0%)	1.000
Weight loss	45	3/23 (13.0%)	2/22 (9.1%)	1.000
URI symptoms	53	8/33 (24.2%)	7/20 (35.0%)	0.399
Increased size when followed up	69	11/37 (29.7%)	15/32 (46.9%)	0.143
Tuberculosis contact	57	3/26 (11.5%)	5/31 (16.1%)	0.715
Size (cm) [median, IQR]	87	1.5 (1.5)	2 (1.5)	0.058

Table 4. (Cont.) Clinical characteristics of lymphadenopathy in the non-granulomatous and granulomatous lymph nodes group.

		Non-granulomatous lymph node	Granulomatous lymph node	*P*-value
	N	Frequency (%) or mean (SD)	Frequency (%) or mean (SD)	
Location	87			< 0.0001 *
Cervical		30/51 (58.8%)	7/36 (19.4%)	
Submandibular		5/51 (9.8%)	18/36 (50.0%)	
Supraclavicular		10/51 (19.6%)	4/36 (11.1%)	
Others		6/51 (11.8%)	7/36 (19.4%)	
Consistency	65			0.639
Soft		6/35 (17.1%)	3/30 (10.0%)	
Firm		12/35 (34.3%)	15/30 (50.0%)	
Rubbery		14/35 (40.0%)	10/30 (33.3%)	
Hard		3/35 (8.6%)	2/30 (6.7%)	
Fixed lymph node	56	6/37 (16.2%)	5/19 (26.3%)	0.481
Tenderness	70	11/41 (26.8%)	12/29 (41.4%)	0.202
Abnormal CXR	51	13/38 (34.2%)	7/32 (21.9%)	0.255
PPD skin test positive	43	2/16 (12.5%)	16/27 (59.3%)	0.003*
Hemoglobin (g/dL)	49	11.3 (1.7)	11.4 (2.0)	0.882
Hematocrit (%)	49	34.6 (5.0)	35.0 (5.7)	0.795
Platelet count (cell/mm^3)	49	33,6645.2 (119,796.6)	375,833.3 (86,865.2)	0.231
WBC (cell/mm^3)	49	9,958.7 (5407.0)	9,962.8 (3,325.8)	0.776
Neutrophil count (%)	49	50.8 (17.8)	50.4 (15.3)	0.947
Absolute neutrophil count (cell/mm^3)	49	4,909.0 (3813.3)	5,011.1 (2,218.4)	0.918
Lymphocyte count (%)	49	39.5 (17.8)	40.8 (15.4)	0.803
Absolute lymphocyte count (cell/mm^3)	49	3,747.1 (2767.0)	4,097.2 (2185.7)	0.648

* $P < 0.05$ indicates statistical significance.

Table 5. Odds ratio for predictive factors for malignant lymph node from univariate and multivariate logistic regression models.

	Univariate analysis		Multivariate analysis	
	Crude odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Duration	0.2 (0.1–1.1)	0.061	0.3 (0.0–2.7)	0.263
Fever	6.0 (1.6–22.4)	0.008	1.1 (0.1–10.8)	0.947
Location				
Cervical	Reference		Reference	
Submandibular	-		-	
Supraclavicular	14.9 (3.3–67.0)	< 0.001	9.1 (0.9–97.4)	0.067
Others	0.7 (0.1–6.8)	0.748	1.0 (0.1–14.9)	0.971
Abnormal CXR	36.0 (6.8–191.9)	< 0.001	8.8 (0.8–94.0)	0.072

Comparisons between non-malignant and malignant lymph node groups

Table 6. presents a comparison of patient clinical characteristics between non-malignant and malignant lymph node groups. Statistically significant differences were observed between these groups in terms of duration, fever, lymph node location, abnormal chest x-ray, neutrophil percentage, and lymphocyte percentage. In the malignant lymph node group, the supraclavicular area was the most frequently involved site (64.3%), while no malignant lymph nodes are found in the submandibular area.

A logistic regression model for predicting malignant lymph nodes was developed using four variables. Descriptive statistics for these variables are summarized in **Table 5.** Univariate analysis revealed that malignant lymph nodes were associated with fever (OR, 6.0; 95% CI, 1.6–22.4; $P = 0.008$), supraclavicular location (OR, 14.9; 95% CI, 3.3–67.0; $P < 0.001$), and abnormal chest x-ray (OR, 36.0; 95% CI, 6.8–191.9; $P < 0.001$). However, the multivariate logistic regression model showed that none of these variables were significant independent predictors of malignant lymph nodes.

Discussion

Lymphadenopathy is a frequent finding in children and often presents a diagnostic challenge for clinicians.[1] It can be a symptom of various diseases.[2] Enlargement of lymph nodes may result from reactive, infectious, or malignant causes.[1] Although surgical biopsy often provides a definitive diagnosis, it may not be necessary in all cases.[1] Deciding which children should undergo excisional biopsy requires careful consideration to avoid unnecessary procedures while also preventing delays in diagnosing malignancy.[7]

This study was conducted in Thailand, a developing country. The results showed that 36 out of 87 patients (41.4%) who had surgical biopsy had granulomatous lymph nodes, a notably higher incidence compared to other countries. A systematic review of 2,687 pediatric patients with cervical lymphadenopathy from five countries by Deosthali A, *et al*.[8] reported granulomatous causes in 109 patients (4.1%), with tuberculosis being the most common (73.4%), followed by atypical mycobacteria (22.9%) and nonspecific granulomatous disease (3.7%). Similarly, a retrospective study in South Africa by Moore SW, *et al*.[4] found chronic granulomatous changes in 484 of 637 (36.3%) cervical lymph node biopsies in children, with tuberculous lymphadenitis confirmed in 332 cases (25.0%). The high incidence of granulomatous disease in these studies aligns with our findings, although our study identified four cases of nontuberculous lymphadenitis, whereas Moore SW, *et al.* did not detect mycobacteria other than *M. tuberculosis*.

In our study, lymphoma was the most common cause in the malignant lymph node group, which is consistent with findings from other studies.[4, 8] PTLD was also a frequent cause in this group, occurring in

Table 6. Odds ratio for predictive factors for granulomatous lymph node from univariate and multivariate logistic regression models.

	Univariate analysis		Multivariate analysis	
	Crude odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Overlying skin redness (OSR)	13.8 (2.6–73.4)	0.002	8.0 (1.1–58.8)	0.040
Fever	0.3 (0.1–0.9)	0.035	0.5 (0.1–3.0)	0.411
Location				
Cervical	Reference		Reference	
Submandibular	15.4 (4.3–55.9)	< 0.001	9.7 (1.3–72.1)	0.027
Supraclavicular	1.7 (0.4–7.1)	0.457	2.6 (0.2–47.1)	0.511
Others	5.0 (1.3–19.6)	0.021	8.3 (0.7–93.7)	0.088

all four patients with biliary atresia who had undergone liver transplantation. PTLD comprises a varied group of potentially life-threatening malignant or premalignant disorders that develop within the hematopoietic system. In children, PTLD is most often linked to Epstein-Barr virus. Histologic confirmation of PTLD is generally advised when lymphadenopathy or an extranodal mass is present. Moreover, complete surgical removal may serve as an effective treatment for localized PTLD.[9] Therefore, pediatric patients with a history of solid organ transplantation presenting with lymphadenopathy should have a lymph node biopsy performed by complete excision.

Several studies have identified factors linked to malignant lymph nodes. A prospective clinical cohort study by Bozlak S, *et al*.[10] reported that cervical lymphadenopathy larger than 30 mm, rubbery lymph nodes, elevated serum CRP and LDH levels, absence of hilum on ultrasonography, and lymph node enlargement on follow-up were predictive of malignancy. A retrospective study by Celenk F, *et al*.[11] found that older age, male gender, larger lymph node size, and left-sided lymphadenopathy were significant predictors of malignancy. Another retrospective study by Wang J, *et al*.[12] showed that a higher ratio (> 0.5), involvement of multiple cervical regions (≥ 2), and location of the largest node in region II or III were associated with malignancy. However, in developing countries like Thailand, granulomatous causes, including tuberculous and nontuberculous lymphadenitis, are the predominant reasons for cervical lymphadenopathy in children. Therefore, identifying predictive factors for LNFM, which includes both granulomatous and malignant lymph nodes, may help prevent unnecessary surgeries and avoid delays in necessary surgical treatment in developed countries.

Comparisons Between Non-LNFM and LNFM Groups

Clinical factors linked to LNFM include OSR, symptoms of URI, increase in size during follow-up, lymph node size, lymph node location, fixed lymph node, positive PPD skin test, and abnormal chest x-ray. Therefore, a patient with clinically diagnosed cervical lymphadenopathy displaying these features should have a biopsy. Regarding lymph node location, 18 of 23 submandibular nodes were LNFM, and all of these were granulomatous lymph nodes. Among 14 patients with supraclavicular nodes, 9 (64.3%) had malignant lymph nodes, 4 (28.6%) had granulomatous lymph nodes, and 1 (7.1%) was diagnosed with Kikuchi-Fujimoto disease. These findings are consistent with a study by Indolfi P, *et al*. [13], who reported that 22 (81.4%) of 27 cases with supraclavicular lymphadenopathy were of neoplastic origin. Thus, supraclavicular lymph nodes of any size should be considered highly suspicious for malignancy.

Comparisons Between Non-granulomatous and Granulomatous Lymph Node Groups

Clinical factors associated with granulomatous lymph nodes include OSR, absence of fever, lymph node location, and positive PPD skin test. Within the granulomatous lymph node group, the most common site was the submandibular area (50.0%). The history of tuberculosis contact and abnormal chest x-ray were not linked to granulomatous lymph nodes; only 5 of 31 (16.1%) patients in this group had a history of tuberculosis contact, and only 7 of 32 (21.9%) showed abnormal chest x-ray. Among 15 cases of tuberculous lymphadenitis, 3 (20.0%) had disseminated tuberculosis with pulmonary involvement. This suggests that tuberculous lymphadenitis in children can develop even without clear exposure to a tuberculosis patient and usually without pulmonary involvement. These findings align with a cross-sectional study by Shah I, *et al*.[14] involving 63 patients with tuberculous cervical lymphadenopathy, where 25 of 63 (39.7%) had a history of contact with a tuberculosis patient, 5 of 63 (7.9%) had pulmonary tuberculosis, 4 of 63 (6.3%) had mediastinal lymphadenopathy, and 1 of 63 (1.6%) had disseminated tuberculosis. Another granulomatous cause is nontuberculous lymphadenitis, for which mycobacterial culture is the diagnostic gold standard, although its sensitivity is 67.2%.[6]

At our institute, lymph nodes diagnosed pathologically as granulomatous lymph nodes with negative mycobacterial culture may be classified as provisional nontuberculous *Mycobacterium* lymphadenitis after excluding tuberculous lymphadenitis. Studies by Loizos A *et al*.[15] and Gracia-Marcos PW, *et al*.[16], conducted on children with culture-positive lymphadenitis caused by nontuberculous mycobacteria, found that the most frequently isolated nontuberculous mycobacteria was *Mycobacterium avium*, accounting for 17/22 (77.3%) and 20/24 (83.3%), respectively. These findings differ from our study, where no *Mycobacterium avium* was isolated.

Comparisons between non-malignant and malignant lymph node groups

Clinical factors linked to malignant lymph nodes include fever, lymph node location, abnormal chest x-ray, neutrophil percentage, and lymphocyte percentage. In the malignant lymph node group, the most common location was the supraclavicular area (64.3%), and no malignant lymph nodes were found in the submandibular area. Our findings do not align with studies by Bozlak S, *et al.*[10], Celenk F, *et al.*[11], and Wang J, *et al.*[12], possibly because our patient population has a higher proportion of granulomatous cases and a lower proportion of malignant cases compared to those studies.

As our study is retrospective, many medical records had missing data, leading to the exclusion of some variables from the logistic regression analysis. Ultimately, we identified submandibular location and abnormal chest x-ray as important predictors for LNFM. Lymph nodes larger than 2 cm were more likely to be LNFM. OSR and submandibular location were indicators of granulomatous pathology. Although no clinical factors were independent predictors of malignant lymph nodes, most supraclavicular nodes were LNFM, indicating a high rate of malignancy. These clinical findings are summarized in the infographic shown in **Figure 2**. This information can assist clinical decision-making before biopsy in patients with clinically diagnosed cervical lymphadenopathy.

In this study, we evaluated several clinical factors to enhance the prediction of LNFM, granulomatous lymph nodes, and malignant lymph nodes. These factors can be readily obtained from a patient's medical history, physical examination, laboratory tests, or radiologic evaluations when cervical lymphadenopathy is clinically diagnosed. Applying these factors may assist in guiding the management of cervical lymphadenopathy. However, this study has limitations, including its retrospective design, small sample size, and differing prevalence of granulomatous lymph nodes across countries with varying healthcare systems. A larger prospective study may help identify additional clinical factors for predicting LNFM.

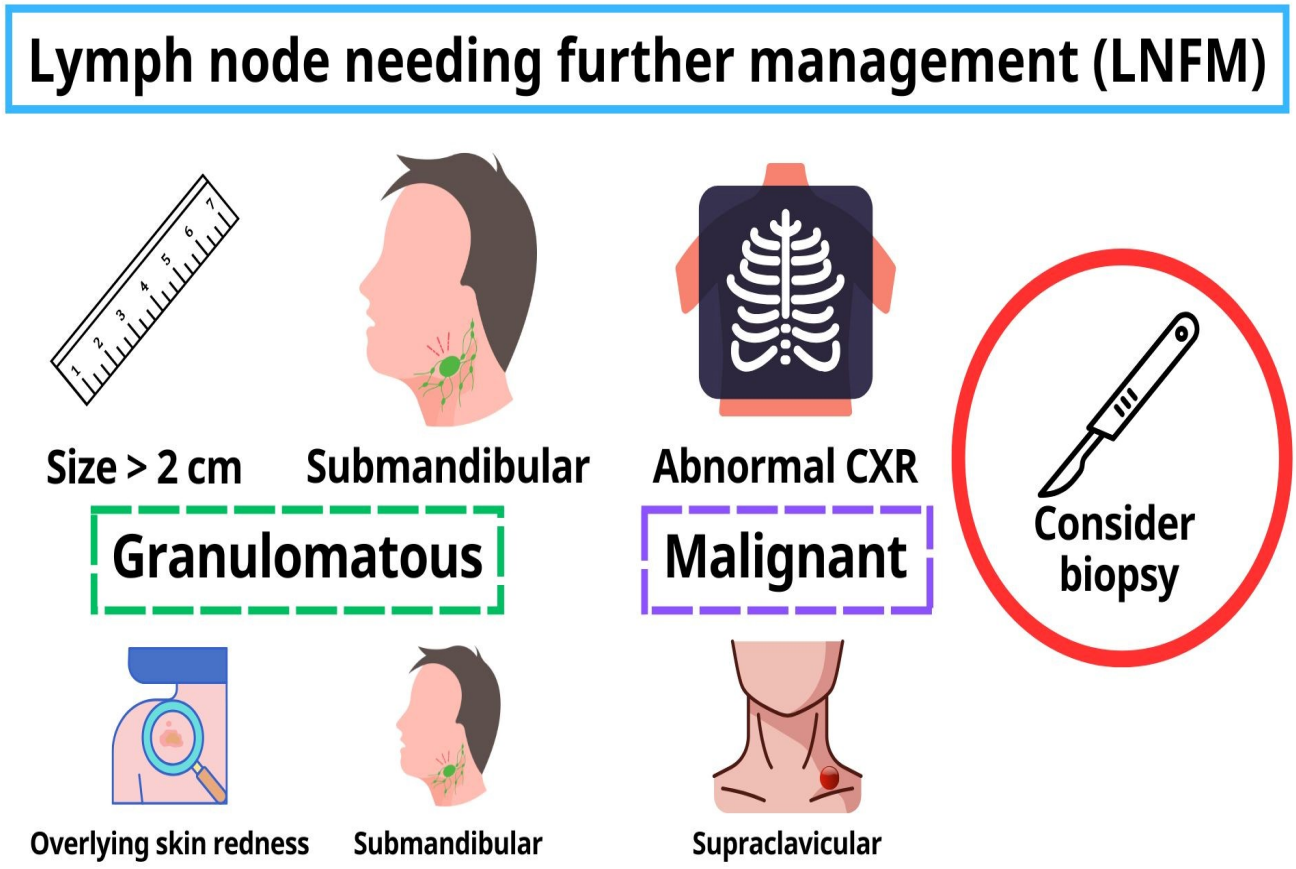

Figure 2. The infographic summarizes the characteristics of the lymph node needing further management (LNFM), for which biopsy is recommended.

Conclusion

Submandibular location and abnormal chest x-ray are significant predictors of LNFM. Lymph nodes larger than 2 cm are more likely to be LNFM. Additionally, OSR and submandibular location indicate granulomatous pathology. Most supraclavicular nodes were LNFM, with a high rate of malignancy, emphasizing the need for careful attention to this area. These findings can support clinical judgment prior to biopsy in patients with clinically diagnosed cervical lymphadenopathy.

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Conflict of interest statement

The author has completed and submitted the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors report any conflicts of interest.

Data sharing statement

All data generated or analyzed in this study are included within this published article. Additional details are available for non-commercial purposes from the corresponding author upon reasonable request.

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