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Usefulness of lactate dehydrogenase in differentiating abnormal cervical lymphadenopathy

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Abstract

Background: Cervical lymphadenopathy is commonly seen in general practice, and its etiology is diverse. Establishing the diagnostic strategy for lymphadenopathy would be desirable to avoid overlooking neoplasms or other critical conditions. This study aims to identify the useful laboratory parameters for cervical lymphadenopathy that require clinical observation or intervention.

Methods: The participants were outpatients presenting cervical swelling or cervical lymph node (LN) pain who consulted the General Internal Medicine department from 2010 to 2016. We evaluated the characteristics, physical findings, and laboratory parameters with final diagnoses by multivariate logistic regression analysis. We categorized the final diagnoses as "Clinical Intervention Required Group (CIRG)" including necrotizing lymphadenitis, hematologic neoplasms, metastatic lymphadenopathy, tuberculous lymphadenitis, bacterial infectious diseases, infectious mononucleosis, autoimmune diseases, and other abnormal conditions or "No-CIRG" not requiring further clinical observation or intervention.

Results: We evaluated 409 participants, with 130 (31.8%) diagnosed as belonging to the CIRG. There was an association between CIRG and various parameters: age ≥60 years old (adjusted odds ratio [AOR], 2.70; 95% confidence interval [CI], 1.48-4.90), having a referral (AOR, 1.83; 95% CI, 1.12-3.00), diameter of LN ≥ 2 cm (AOR, 1.91; 95% CI, 1.05-3.48), fixed LNs (AOR, 2.74; 95% CI, 1.02-7.37), and lactate dehydrogenase (LD) ≥400 U/L (AOR, 3.78; 95% CI, 1.46-9.77). Eighty-two percent of LD ≥ 400 cases in the CIRG were infectious mononucleosis or necrotizing lymphadenitis.

Conclusions: Besides the clinical indicators reported previously, we may apply an elevated LD level as a useful indicator of cervical lymphadenopathy that requires further clinical observation or intervention.

KEYWORDS

cervical lymphadenopathy, diagnosis, lactate dehydrogenase, lymph node

1 | INTRODUCTION

Lymphadenopathy is a common sign encountered in daily clinical practice. Although the incidence of neoplasms in patients with lymphadenopathy in a primary care setting is as low as 1% to 2%,[1] the etiology of the lymphadenopathy other than neoplasms consists of various categories: infection, autoimmune disorder, and idiopathic disorder.[2] Overlooking neoplasms or other conditions which require medical intervention must be avoided, and so establishing the optimal diagnostic method for patients with lymphadenopathy would be desirable.

Several studies have focused on the clinical indicators in the subjects diagnosed with neoplasms or requiring lymph node (LN) biopsy in patients with lymphadenopathy. Fijten et al[1] reported that patients with lymphadenopathy aged over 40 years with an enlarged supraclavicular LN were most likely to have a neoplasm. Vassilakopoulos et al[3] developed a scoring system using six variables: age over 40 years, absence of tenderness, size of 1 cm^2 or more, generalized pruritus, supraclavicular location, and hard texture to identify the patients who require biopsy in the hematology clinic. Chau et al[4] reported that the five predictors for diagnosing LN associated with neoplasms were male gender, higher age, white ethnicity, LN located in the supraclavicular region, and involvement of 2 regions or more in the tertiary referral comprehensive cancer center. However, those studies were conducted in specialized institutions rather than in the general practice setting.

The head and neck region is the most frequent location where swollen LNs are observed.[4,5] Patients with neck swelling tend to visit general practitioners first, because of anxiety about serious diseases and the low medical expense supported by the Japanese public health insurance system. Our institution provides not only advanced medical care but also primary care for the local community. From the viewpoint of cost-effectiveness of examinations, it is reasonable to use suitable clinical indicators especially in the general practice setting with a low pretest probability of harboring LN that would require clinical intervention. Although medical interview and physical examination are the starting points for the diagnosis, basic laboratory examinations also facilitate the clinical reasoning for each patient.[6,7]

The objective of this study is to clarify the useful laboratory parameters in addition to clinical characteristics or physical findings in patients with cervical lymphadenopathy that indicate a need for further clinical intervention in general practice. We selected lactate dehydrogenase (LD) and C-reactive protein (CRP) as candidates of laboratory parameters, because LD is a basic practical laboratory marker in general practice, and CRP reflects inflammation of various tissues.

2 | MATERIALS AND METHODS

2.1 | Study design, setting, and participants

We conducted a retrospective observational study for the patients presenting cervical swelling or cervical LN pain. Participants were recruited from new outpatients who consulted the General Internal Medicine (GIM) department of Jichi Medical University Hospital from June 2010 to December 2016. The GIM department provides care for patients with a variety of health problems and symptoms of unknown origin. According to the referral, the outpatients are then referred to the department deemed most appropriate. The outpatients without a referral are guided to the information office where a physician suggests the most appropriate department according to their complaints. If patients seem to require an evaluation by generalists, they are guided to the GIM department. In general, patients presenting cervical lymphadenopathy of unknown origin consult the GIM department.

The number of new outpatients during this period was 12,379. We reviewed the medical records and identified the 458 participants who presented cervical swelling or cervical LN pain. We excluded patients who had only cervical pain from musculoskeletal conditions without cervical swelling (number [n] = 36). We also excluded those with cervical nodes that were not LN (n = 9) and returning patients with the same sign (n = 4). The final number of eligible participants for this study was 409 (Figure 1).

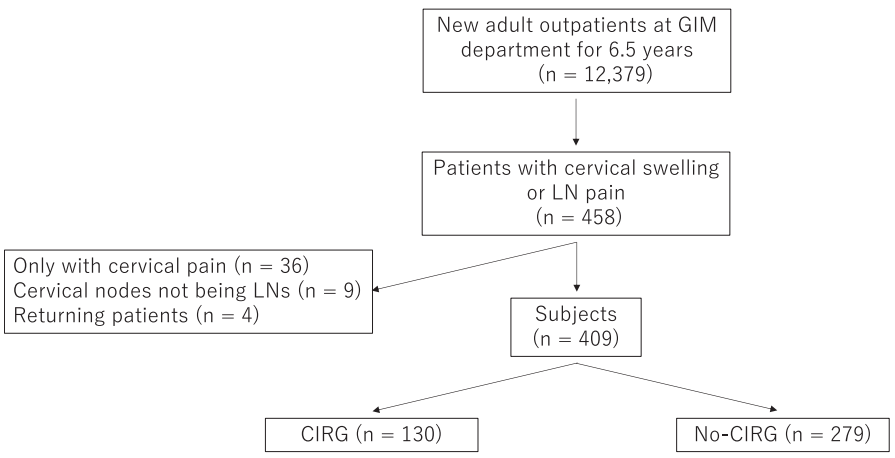

FIGURE 1 Flowchart of participants. Abbreviations: CIRG, Clinical Intervention Required Group; GIM, General Internal Medicine; LN, lymph node; n, number

2.2 | Measurements

We evaluated characteristics, symptoms, physical findings, laboratory parameters, and diagnoses from the medical records. Characteristics of the participants were gender, age, with or without a referral, and course. Symptoms were fever, chill, night sweats, weight loss, malaise, headache, sore throat, cough, nausea, abdominal pain, and diarrhea. Physical findings were temperature, pulse rate, blood pressure, and the following characteristics of LN: location, number, diameter, shape, texture, the presence of pain, tenderness, and mobility. Laboratory parameters were white blood cell counts, hemoglobin, platelet counts, aspartate aminotransferase, alanine aminotransferase, LD, CRP, and soluble interleukin-2 receptor. The laboratory data excluding the soluble interleukin-2 receptor were obtained at the first visit. The soluble interleukin-2 receptor was obtained at the first visit or after the second visit when necessary. The final diagnoses were determined by reviewing the results of blood tests, ultrasonography, computed tomography, histological diagnosis of fine-needle aspiration or biopsy, or other medical findings. Six physicians practicing in the outpatient clinic of the GIM department extracted these parameters from the medical records. Symptoms not noted in the medical records were considered not to be present in the patient. Physical findings unstated on medical records and unmeasured laboratory parameters were considered to be missing values. Three of the six physicians checked all final diagnoses for accuracy and categorized all patients into either a "Clinical Intervention Required Group (CIRG)" or "No-CIRG". We defined "CIRG" as the subjects who required close observation or clinical intervention. Clinical intervention represents some diagnostic procedures or treatment such as analgesics, antibiotics, steroids, or anticancer agents. The diagnostic procedures include computed tomography, magnetic resonance imaging, positron emission tomography, or LN biopsy. We defined "No-CIRG" as those who did not require further observation or clinical intervention. The CIRG includes the following eight categories: necrotizing lymphadenitis; hematologic neoplasms such as lymphoma, leukemia, or plasmacytoma; metastatic lymphadenopathy; tuberculous lymphadenitis; bacterial infectious diseases; infectious mononucleosis; autoimmune disease; and others which require clinical intervention. Others in CIRG include tumor or inflammation of the parotid gland and submandibular gland, nodule of the thyroid, cellulitis, erysipelas, folliculitis, lipoma, lymphangioma, Schwannoma, and insect sting. The No-CIRG includes following normal or reactive LN; viral infection, upper respiratory infection, dental caries, external otitis, parotitis, cellulitis, trauma, reaction to a vaccine, normal tissues such as vessels, muscles, submandibular gland, cervical rib, and cricoid cartilage.

2.3 | Statistical analysis

The chi-squared test for nominal variables and the Student's *t* test for continuous variables were employed for a comparison of characteristics, physical findings, and laboratory parameters between the CIRG and No-CIRG. Continuous variables were transformed into categorical intervals, and we analyzed the association between variables and the CIRG by multivariate logistic regression analysis. Variables for multivariate logistic regression analysis included gender, age, with or without a referral, and variables of physical findings and laboratory parameters with clinical importance or a significant difference in univariate logistic regression analysis. Continuous variables in the multivariate logistic regression analysis were defined as age ≥60 years, number of cervical LNs ≥ 6, diameter of LNs ≥ 2 cm, LD ≥ 400 U/L (normal: 124-222 U/L), and CRP ≥ 3 mg/dL (normal: 0.00-0.14 mg/dL). The odds ratio and 95% confidence intervals (CI) were calculated to evaluate the risk of the CIRG for the participants with each clinical feature. We used the imputed data set from multiple imputations for multivariate logistic regression, because physical findings and laboratory parameters had missing values.

The statistical analyses were performed using SPSS version 21.0 (IBM Corporation) computer software package and SAS 9.4 (SAS Institute Inc) for multiple imputations.

TABLE 1 Comparison of clinical features between CIRG and No-CIRG

	CIRG (n = 130; 31.8%)	No-CIRG (n = 279; 68.2%)	*P*-value
Men	46 (35.4%)	96 (34.4%)	.847†
Mean Age	46.2 ± 19.8	37.2 ± 15.9	<.001‡
60 years or more	42 (32.3%)	38 (13.6%)	<.001†
With a referral	84 (64.6%)	119 (42.7%)	<.001†

Note: Data are shown as the mean ± standard deviation or percentage. The comparison among participants classified as CIRG or No-CIRG was performed by †chi-squared test; ‡Student's *t* test.

Abbreviations: CIRG, Clinical Intervention Required Group; n, number.

2.4 | Ethics

The institutional review board of Jichi Medical University approved this study.

3 | RESULTS

A total of 409 participants with cervical swelling or cervical LN pain were enrolled in this study. 267 (65.3%) participants were women and 142 (34.7%) were men. The participants' ages ranged from 15 to 88 years (mean age: 40.0 ± 17.7 years), and 80 (19.6%) of the 409 participants were 60 years old or more. Of all the participants, 203 (49.6%) were referred by other medical institutions.

There was no difference in the ratio of men to women between the CIRG and No-CIRG (Table 1). The mean age of the CIRG was older than that of No-CIRG (46.2 ± 19.8 vs 37.2 ± 15.9, $P < .001$). The percentage of participants 60 years old or more in the CIRG

was higher than that in the No-CIRG (32.3% vs 13.6%, $P < .001$). The ratio of participants with referral was higher in the CIRG (64.6% vs 42.7%, $P < .001$).

A total of 130 (31.8%) participants were assigned to the CIRG (Table 2). Twenty-seven (6.6%) and twenty participants (4.9%) were diagnosed with necrotizing lymphadenitis and infectious mononucleosis, respectively. Thirty-one (7.5%) participants had neoplasms, diagnosed as metastatic lymphadenopathy (n = 19) or hematologic neoplasms (n = 12). Forty-three (10.5%) participants were diagnosed with other conditions. No-CIRG includes other normal tissues (n = 10, 2.4%) and unclassifiable LN (n = 3, 0.7%).

The risk factors associated with being classified to the CIRG according to the clinical features, physical findings, and laboratory parameters by multivariate analysis were age ≥ 60 years (adjusted odds ratio [AOR], 2.70; 95% CI, 1.48-4.90), having a referral (AOR, 1.83; 95% CI, 1.12-3.00), diameter of cervical LN ≥ 2 cm (AOR, 1.91; 95% CI, 1.05-3.48), fixed cervical LNs (AOR, 2.74; 95% CI, 1.02-7.37), and LD ≥ 400 U/L (AOR, 3.78; 95% CI, 1.46-9.77) (Table 3). The data for gender, 60 years or more, and having a referral were complete. Missing values were 22.5% for the number of cervical LNs ≥ 6, 24.7% for the diameter of cervical LN ≥ 2 cm, 33.0% for the absence of tenderness in LNs, 45.7% for fixed cervical LNs, 25.7% for LD ≥ 400 U/L, and 27.4% for CRP ≥ 3 mg/dL.

Table 4 shows the median value of LD and 25th and 75th percentiles for each final diagnosis. The median values of LD were 201.0 U/L for the CIRG and 181.0 U/L for the No-CIRG. The six higher median values of LD for the final diagnosis were 403.5 U/L for infectious mononucleosis, 257.0 U/L for necrotizing lymphadenitis, 231.5 U/L for autoimmune disease, 220.0 U/L for bacterial infection, 208.0 U/L for hematologic neoplasms, and 200.0 U/L for metastatic lymphadenopathy. The number of participants with an LD level of 400 U/L or more in the CIRG was higher than that in No-CIRG. Seventeen participants in the CIRG showed an LD level of 400 U/L or more: 9 (52.9%) infectious mononucleosis; 5 (29.4%) necrotizing lymphadenitis; 2 (11.8%) metastatic lymphadenopathy; and 1 (6.2%) hematologic neoplasm.

TABLE 2 Final diagnosis in 409 participants

Final diagnosis	n	%
CIRG	130	31.8
Necrotizing lymphadenitis	27	6.6
Infectious mononucleosis	20	4.9
Neoplasms		
Metastatic lymphadenopathy	19	4.6
Hematologic neoplasms	12	2.9
Tuberculosis	4	1.0
Bacterial infection	3	0.7
Autoimmune disease	2	0.5
Others	43	10.5
No-CIRG	279	68.2

Abbreviations: CIRG, Clinical Intervention Required Group; LN, lymph node; n, number.

The proportion of the total of infectious mononucleosis (n = 9) and necrotizing lymphadenitis (n = 5) out of the cases with LD ≥ 400 in the CIRG (n = 17) was 82.4%.

4 | DISCUSSION

In our study, lymphadenopathy needing clinical interventions was associated with age ≥ 60 years, being referred, diameter of LNs ≥ 2 cm, fixed cervical LNs, and LD ≥ 400 U/L. Although some previous studies reported that age, referral, LN size, and fixed LN were useful parameters in differentiating neoplastic or granulomatous cervical lymphadenopathy from other conditions, they reported clinical indicators for cervical lymphadenopathy in participants receiving LN biopsy or final diagnosis of neoplasms. Developing a scoring system was studied, although it was to identify patients receiving LN biopsy.[3,8]

In this study, an LD level of 400 U/L or more was associated with the CIRG independently and LD level tended to be 400 U/L or more in patients with infectious mononucleosis and necrotizing lymphadenitis. An elevated LD level is a well-known finding in non-Hodgkin lymphoma or leukemia.[9,10] However, it is also seen in various other clinical conditions, because LD derives from various tissues, for example, muscle, liver, kidney, and hemopoietic cells. An elevated LD level in necrotizing lymphadenitis has been found in many studies and is one of the most frequently observed laboratory findings.[11–13] It is a marker of severe inflammation or necrotic lesion. It is also found in more than half of patients with infectious mononucleosis, signifying liver damage.[14] Furthermore, an elevated LD level is seen in various neoplasms, particularly in the metastatic stage.[15] This tendency was not seen in our study, because the number of patients with neoplasm, especially at an advanced stage, was small. A statistically significant association between a high level of LD and neoplasms was also obtained in a previous study for cervical lymphadenopathy, which, however, targeted participants undergoing lymphadenectomy.[16] The result of our analysis suggests that an elevated LD level also contributes to distinguishing LN for CIRG. A careful examination should be conducted for patients with cervical lymphadenopathy showing an elevated LD level, keeping in mind that neoplasms cannot be excluded simply because the LD level is low. According to the data from our study, nine of ten cases of neoplasm would be overlooked, if the cutoff value of LD level was to be set at 400 U/L.

Age has been indicated as the most important factor in predicting neoplastic or benign etiology of lymphadenopathy because of the higher prevalence of neoplasms in aged patients.[1,5,17,18] The prevalence of neoplasms was reported to rise from 1.1% to 17.3% in patients with a referral.[1,4] The patients with a referral have already been assessed by a physician at the initial medical institution. A normal cervical LN size is usually <1 cm in diameter.[19,20] There is no definite size of LN that can indicate neoplasms or granulomatous diseases, although a diameter over 1.5 or 2 cm was considered to be neoplastic or granulomatous LNs in previous reports.[21,22] LN fixed to the skin or surrounding tissues is highly

TABLE 3 Risk of CIRG according to the clinical features, physical findings, and laboratory parameters by multivariate analysis

	N	n	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*-value
Gender (men)	409	142 (34.7%)	1.04 (0.67-1.61)	0.93 (0.56-1.53)	.761
60 years or more	409	80 (19.6%)	3.03 (1.83-5.00)	2.70 (1.48-4.90)	.001*
Having a referral	409	203 (49.6%)	2.46 (1.60-3.78)	1.83 (1.12-3.00)	.017*
Number of cervical LNs ≥ 6	317	41 (12.9%)	1.36 (0.68-2.74)	1.13 (0.50-2.53)	.773
Diameter of LNs ≥ 2 cm	308	99 (32.1%)	4.06 (2.41-6.82)	1.91 (1.05-3.48)	.036*
Absence of tenderness in LNs	274	146 (53.3%)	1.06 (0.63-1.77)	1.03 (0.59-1.83)	.909
Fixed cervical LNs	222	23 (10.4%)	16.26 (5.26-50.23)	2.74 (1.02-7.37)	.046*
LD ≥ 400 U/L	304	24 (7.9%)	5.30 (2.12-13.24)	3.78 (1.46-9.77)	.006*
CRP ≥ 3 mg/dL	297	39 (13.1%)	2.00 (1.12-4.38)	1.61 (0.75-3.44)	.221

Abbreviations: CI, confidence interval; CIRG, Clinical Intervention Required Group; CRP, C-reactive protein; LD, lactate dehydrogenase; LN, lymph node; n, number of subjects with positive findings; N, number of total subjects whose findings were obtained; OR, odds ratio.

*P-value < .05.

TABLE 4 Median value of LD for each final diagnosis

Final diagnosis	N	n (with LD ≥ 400 U/L)	Median value of LD (U/L) (25%, 75%)
CIRG	105	17 (16.2%)	201.0 (169.0, 291.0)
Necrotizing lymphadenitis	25	5 (20.0%)	257.0 (188.5, 387.5)
Infectious mononucleosis	18	9 (50.0%)	403.5 (270.0, 511.3)
Metastatic lymphadenopathy	18	2 (11.1%)	200.0 (168.0, 228.3)
Hematologic neoplasms	10	1 (10.0%)	208.0 (151.8, 380.3)
Tuberculosis	2	0 (0.0%)	188.0 (160.0, -)
Bacterial infection	3	0 (0.0%)	220.0 (149.0, -)
Autoimmune disease	2	0 (0.0%)	231.5 (197.0, -)
Others (abnormal)	27	0 (0.0%)	178.0 (153.0, 191.0)
No-CIRG	199	7 (3.5%)	181.0 (157.0, 218.0)

Abbreviations: CIRG, Clinical Intervention Required Group; LD, lactate dehydrogenase; LN, lymph node; N, number of subjects in whom LD level was measured; n, number of subjects with LD ≥ 400 U/L.

associated with neoplasms, while LNs resulting from infection or autoimmune disorder are usually freely movable in the subcutaneous region.[20,23]

In approaching patients with cervical lymphadenopathy, decision making for further diagnostic workup is sometimes difficult. When the clinical findings indicate a high probability of No-CIRG, observation for three to four weeks is an appropriate approach.[24] Clinical findings obtained from the first medical evaluation can help to select an appropriate workup for the patients with cervical lymphadenopathy. Therefore, LD should be measured at the first medical evaluation when unknown cervical lymphadenopathy cannot be diagnosed only by a medical interview and physical examination.

The strength of this study is that the outcome of our study is whether the LN requires clinical intervention or not and is not limited to any specific procedures or conditions. The result of our study can be applied to the decision making for the performance of a further diagnostic workup in the context of daily general practice.

The limitation of our study is that there might be a diagnostic bias, because not all participants were subjected to a LN biopsy as a reference standard examination for the diagnosis. A total of 26 (6.4%) participants had LN biopsies, and the duration from the first visit to

LN biopsy was 50 days (range, 2-274 days). LN biopsy should be performed in cases that are suspected of having neoplasms. Patients diagnosed with necrotizing lymphadenitis are more likely to be biopsied because the LD level tended to be high. Second, the mechanism of elevated LD levels was obscure, because LD isozyme was not evaluated. The elevated LD levels may reflect liver damage in cases of infectious mononucleosis. Third, there were some missing values, because each physician obtained physical findings, conducted laboratory tests, and selected laboratory parameters according to his own judgment. Fourth, 82% of LD ≥ 400 cases in the CIRG were infectious mononucleosis or necrotizing lymphadenitis. There were too few cases to analyze other diseases. Therefore, a prospective study would be desirable.

In conclusion, an elevated LD level might be a useful hallmark in the diagnostic process of lymphadenopathy, in addition to the clinical indicators reported previously. Eighty-two percentage of LD ≥ 400 cases in the CIRG were infectious mononucleosis or necrotizing lymphadenitis. This result might help the early decision making for further observation or performing adequate diagnostic workup for an accurate diagnosis.

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CONFLICTS OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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