Predicting nodal malignancy from clinical data

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ABSTRACT

Objectives A large variety of disorders can lead to lymphadenopathy. It is important and beneficial to patient management to rapidly differentiate between benign and malignant causes. The objective of the study is to identify factors predicting nodal malignancy from readily available clinical data.

Methods A retrospective study was carried out on patients admitted to Riyadh Medical Complex, Riyadh, Kingdom of Saudi Arabia between April 1996 and March 2000 with lymphadenopathy, who underwent lymph node biopsy.

Results Univariate analysis suggests 6 variables (age, sex, the presence of other physical signs, abnormal complete blood count, abnormal liver function test and negative Mantoux test) to have independent association with nodal malignancy. The multivariate logistic regression model revealed patients aged more than 40 years, males, generalized lymphadenopathy, presence of other physical signs, abnormal liver function tests and negative Mantoux test to be statistically significantly associated with nodal malignancy ($p>0.05$).

Conclusion The present logistic model can be useful in predicting nodal malignancy using routinely collected clinical data.

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Clinicians commonly encounter lymphadenopathy (LA) and a population study has reported an annual incidence of 6 per 1000.[1] As many as 56% of patients examined for other reasons were found to have LA.[2] The primary presenting symptoms of a patient with LA usually raises doubt as to whether the LA is benign or malignant. In certain situations, clinicians have adopted a wait-and-see policy, but others require a speedy evaluation and management. A common definitive diagnostic procedure is lymph node biopsy, which is invasive, costly and capable of heightening patient anxiety. In addition, it sometimes leads to misdiagnoses: for instance the histology of certain benign conditions like infectious mononucleosis and drug induced LA may mimic lymphoma.[3-5] However, some studies have suggested that simple, demographic, clinical and laboratory features could differentiate benign from malignant causes. Therefore, the objective of this study was to determine factors associated with nodal malignancy from such simple routinely collected data. This would be beneficial in the diagnostic process.

Methods. The study was a chart review of all patients who presented to Riyadh Medical Complex, Riyadh, Kingdom of Saudi Arabia (KSA), between April 1996 and March 2000 with lymphadenopathy and underwent lymph node biopsy. The demographic, clinical and laboratory information of each patient were extracted into a pre-designed data collection form. The items of information available were patients'age, sex, nationality, duration of symptoms; extension of nodes, other physical signs, complete blood count (CBC), liver function tests (LFTs), Mantoux test and histological

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diagnosis. The diagnosis was further dichotomized into benign and malignant causes as determined by the lymph node biopsy. In a univariate analysis, the association of each variable with nodal malignancy was investigated for statistical significance by the chi-square test. Age was categorized into (less than 40 years or above 40 years, while extension of nodes was dichotomized as either localized or generalized. Lymphadenopathy was considered localized if one group of lymph nodes was involved or generalized if 2 or more non-contagious groups were involved.[6] The duration of symptoms was also categorized into 3 months and below or above 3 months. For each of the categories of the variable, the category with the least risk was described as the reference category for the calculation of the estimate of relative risks. The odds ratio and their 95% confidence intervals were thus calculated for each variable.

Variables significant at the 5% probability level were further included in a logistic regression model in which nodal malignancy serves as the dependent variable. The dependant variable was coded as 1.0 if nodes were malignant and 0 otherwise. So also dummy variables were used for all the independent variables that were described as categorical in the logistic model, which was evaluated by the statistical package for social sciences. The stepwise forward procedure was used, and the Homer-Lemeshow goodness of fit test examined after no more variables satisfied the inclusion criteria in the model.

Results. ***Etiology of lymphadenopathy in the study population.*** One hundred and fifty-six patients had histological features of benign conditions comprising tuberculosis (98), non-specific reactive hyperplasia (36), Kikuchi's disease (7), sarcoidosis (6), dermatopathic LA (3) and one each of 4 other diagnoses. One hundred and two patients presented with malignant lymphadenopathy comprising 85 patients with malignant lymphoma and 17 patients with metastatic disease.

Table 1 shows the association of each variable with nodal malignancy and the 95% confidence intervals of their odds ratio. Patients 40 years and above were 3 times as likely to have nodal malignancy, while males were more than 4 times as likely than females, so also are patients whose lymphadenopathy was generalized. Patients with abnormal CBC or in whom other signs such as pallor, organomegaly, serositis and jaundice were present were approximately 2 times as likely to have nodal malignancy. Patients with negative Mantoux test were more than 15 times as likely to have nodal malignancy while patients with abnormal liver function tests were only 3 times as likely. All these variables were significant at least 1% probability level. The other variables like nationality dichotomized into Saudi and non-Saudi, and duration of symptoms, did not show any statistical significant relationship with nodal malignancy and were therefore not included in the logistic model. The results of the stepwise logistic procedure that models nodal malignancy with these demographic and clinical variables revealed 6 variables to be independently associated with nodal malignancy. The regression coefficients of the variables (age more than 40 years, males, generalized nodes, presence of other physical signs, abnormal liver function and positive Mantoux test) are presented in **Table 2** as well as their estimated relative risks and 95% confidence intervals. The Homer and Lemeshow goodness of fit test gave a chi-square (x^2) value of 9.8171 on 8 d.f and an associated p-value of 0.2781 suggesting the model fits.

The model which showed a positive Mantoux test as protective with an odds ratio of 0.12; 95% CI=0.05–0.28 suggested patients with positive Mantoux test are thus 88% less likely to have nodal malignancy. The next most important predictive variable to positive Mantoux test was presence of other signs followed by male patients and each variable has a risk of more than 250%. Patients 40 years and above and those with generalized lymphadenopathy each has similar 2 and 1/2 times as likely for nodes to be malignant.

The result indicated that the probability of malignant nodes might be predicted from the equation:

$$\Pr(\text{malignant node}) = \frac{1}{1 + e^{-z}}$$

Where Z = -2.1085 + 0.9346 (Age) + 1.2380 (sex) + 0.9546 (extension of nodes) + 1.2741 (other signs) + 0.7193 (LFT) – 2.1348 (Mantoux test)

Where Age = 1 if 40 years and above
Sex = 1 if males
Extension of nodes = 1 if generalized
Other signs = 1 if present
LFT = 1 if abnormal and
Mantoux test = 1 if positive

Thus a male aged 42 years with positive Mantoux test, localized nodes, no other physical signs and a normal LFT has the probability of malignant node calculated as follows:

$$Z = -2.1085 + 0.9346 + 1.2380 - 2.1348 = -2.0707$$

$$\Pr(\text{malignant node}) = \frac{1}{1 + e^{Z}} = \frac{1}{1 + e^{2.0707+}} = \frac{1}{8.93} = 0.1119$$

A man with the same characteristics except that he had a negative Mantoux test, has the probability of nodal malignancy given as:

Table 1 - The association of personal and clinical variables with nodal malignancy.

Variables	n of sample	n with nodal malignancy (%)	Odds ratio	95% CI	p-value
Age group					
<40 years	162	47 (29)	1.00		<0.00001
≥40 years	96	55 (57)	3.28	1.87-5.77	
Sex					
Male	105	63 (60)	4.38	2.49-7.76	<0.00001
Female	153	39 (25)	1.00		
Nationality					
Saudi	145	63 (43)	1.46	0.85-2.50	0.145
Non-Saudi	113	39 (35)	1.00		
Site of nodes					
Localized	162	43 (27)	1.00	2.49-7.86	<0.000001
Generalized	96	59 (61)	4.41		
Signs					
Present	110	69 (63)	5.76	3.22-10.36	<0.00001
Absent	146	33 (23)	1.00		
Complete blood count					
Normal	97	29 (30)	1.00	1.10-344	0.014
Abnormal	161	73 (45)	1.95		
Liver function test					
Normal	122	33 (27)	1.00	1.61-4.95	<0.00001
Abnormal	131	67 (51)	2.82		
Mantoux test					
Positive	94	9 (10)	1.00	6.50-36.86	<0.00001
Negative	105	65 (62)	15.35		
Duration of symptom					
≤3months	177	67 (38)	1.00	0.70-2.20	0.443
>3 months	79	34 (43)	1.24		

CI - confidence interval

$$Z = -2.1085 + 0.9346 + 1.2380. \quad \Pr(\text{malignant node}) = \frac{1}{1+e^{-Z}} = \frac{1}{1.9379} = 0.516$$

Discussion. This study identified 6 variables: age more than 40 years, males, generalized lymphadenopathy, presence of other signs, abnormal liver function tests and a positive Mantoux test to be independently associated with nodal malignancy. The fact that patients over 40 years old were 3 times more likely to have malignancy as the cause of the LA is in consonance with standard teaching[7] and observation from other studies.[8-10] This could be explained by a decrease in cellular immunity, which occurs with aging; a process already shown to predispose to malignancy.[11] Although no strong gender difference is believed to exist in the cause of LA, our study that showed males to be 4 times more likely to have nodal malignancy corroborates one study from the KSA[10] and another from the United Kingdom.[12] In a more recent study; however, gender failed to retain its predictive significance in a multivariate analysis.[13] The proportionately higher rates of malignancy among males in this study can partly be explained by the higher incidence of benign conditions among females. Tuberculosis for example is 4 times more common among females than males and Kikuchi's disease occurred exclusively in females. The latter is probably peculiar to this locality as observed in our earlier study.[14]

A number of systemic diseases may present with generalized LA in addition to easily recognizable signs. Most of such patients might not have been subjected to lymph node biopsies. Patients with generalized LA were found to be 4 times more likely to have nodal malignancy in this study. It is therefore, reasonable to proceed with a lymph node biopsy at an early stage when other features do not readily point to a systemic cause (such as systemic lupus erythematosus) rather than resorting to the less invasive procedure of fine needle aspiration (FNA). This is as FNA, where malignancy is suspected, has a poor yield leading to inability to examine the architecture of the gland[15] and one study has reported a risk of sinus tract formation.[16]

Table 2 - Estimates of regression coefficients of the logistic model of nodal malignancy with demographic and clinical variables.

Variables	(β)	SE (β)	Wald	OR	95% CI
Constant	**-21085**	**0.4171**	**25.5569**		
Age group					
≥40 years	0.9346	0.3669	6.4874	2.55	1.24-5.23
<40 years	0.00			1.000	
Gender					
Male	1.2380	0.3513	12.4204	3.45	1.73-6.87
Female	0.0000			1.00	
Site of nodes					
Generalized	0.9546	0.3567	7.1616	2.60	1.29-5.23
Localized					
Signs					
Present	1.2741	0.3511	13.1657	3.58	1.80-7.12
Absent					
Liver function test					
Abnormal	0.7103	0.3639	3.8099	2.03	1.00-4.15
Mantoux test					
Positive	-2.1348	0.4319	24.43	0.12	0.05-0.28

OR - odds ratio, CI - confidence interval, β - beta, SE - standard error of mean

The association of nodal malignancy with the presence of other physical signs and abnormalities in hematological and biochemical parameters is less impressive. This underlines the significant overlap between benign and malignant conditions in presenting with other signs and in causing hematological and biochemical abnormalities. Mantoux test however had a strong negative predictive value. A patient presenting with LA whose Mantoux test is negative in this environment has a 15 times likelihood of having a nodal malignancy. Tuberculin anergy has been documented in many malignancies[17,18,19] and the Mantoux test has been found to be helpful in predicting nodal malignancy.[20] In our patients, the duration of LA did not correlate with a benign or malignant etiology the 2 most common causes one benign (tuberculosis) and the other malignant (lymphoma), are both capable of exhibiting a prolonged course.

Similarly, nationality had no statistically significant correlation with benign or malignant cause of LA. Some studies have considered the consistency and size of the enlarged lymph nodes in differentiating benign from malignant causes or in deciding on a lymph node biopsy.[10,13] The inherent subjectivity in the documentation of such parameters precluded their use in this retrospective study. Similarly, certain radiological investigations such ultrasonography and computerized tomography scan, although found to be helpful in differentiating between benign and malignant causes of LA,[10,21] may not be readily available to some clinicians. The pattern of disease in this locality may perhaps limit the validity of this instrument in other areas. Moreover, there may be existing policies in different countries regarding the approach to this common clinical condition. However, in KSA and other nations with similar disease pattern, the use of this model may obviate the need for more invasive procedures.

In conclusion, this model, based on readily available demographic and clinical data, can be used to predict the probability of malignancy in patients presenting with LA. However, there is a need to further assess the value of these and other certain clinical features hypothesized to be beneficial in differentiating between benign and malignant causes of LA in a prospective study.

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