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Ultra-Sonographic Cut-off points of Cervical lymph nodes size and shape index in Hodgkin's and Non-Hodgkin's lymphoma

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Abstract: Cervical lymph nodes (CLN) are frequently involved. there is no agreement on which cut-off point for lymph node size should be used in routine clinical practice to differentiate between cervical lymphadenopathy and normal CLN, that the optimal cut-off point of nodal size varies with the patient population. Aim of the study is to estimate Gray-scale Ultra-Sound (US) Cutoff Points of cervical lymph nodes (CLN) size and shape index of lymphomatous CLN of Hodgkin's lymphoma(HL), Non Hodgkin's lymphoma (NHL) groups in contrast to normal CLN in healthy Iraqi persons, and evaluate the difference among studied groups. This study involved 25 patients with HL, 25 with NHL (both with cervical lymphadenopathy) and 25 healthy subjects. all participants were examined using gray scale US machine. The results were : Means of long axis (L) and short axis (S) of NHL (21.47 mm, 13.23 mm) and HL (23 mm, 13.59 mm) were significantly higher than healthy subjects (9.08 mm, 3.85 mm). Means of Short/Long axis ratio (S/L) were (0.634, 0.601, 0.424) mm respectively. Cutoff points for (L) of NHL, HL in contrast to control group were 13.85mm, while they were (5.800 and 7.150) mm for (S) and (0.540 and 0.447)mm for S/L respectively. Gray-scale US Cutoff Points of (L), (S) and S/L had **strong diagnostic strength** in differentiation between lymphomatous CLN and normal CLN in healthy subjects with no significant difference among diseased groups.

Keywords: Cervical lymph node, Gray-scale, Ultra-sound, Hodgkin's, Non Hodgkin's lymphoma

1. Introduction

Cervical lymph nodes are frequently involved in a number of disease conditions, the most commonly seen causes of cervical lymphadenopathy are tuberculosis, distant cancer metastasis and lymphoma in which it is common sites of involvement in HL and NHL patients [1] , and lymphoma may be present as only cervical lymphadenopathy [2]. In the field of Gray-scaled US parameters which used to describe pathological status of lymphnode (L), (S) and S/L come as important parameters to contrast between normal and pathologic lymphnodes, and there is no agreement on which cut-off point should be used in routine clinical practice, furthermore the optimal cut-off point of nodal size varies with the patient population[3]. Early cervical lymphadenopathy diagnosis and early treatment plane leads to good prognosis as many types of lymphoma, especially indolent NHL present with waxing and waning lymphadenopathy for many years [4].

2. Materials And Methods

Study setting

An observational, cross-sectional study was conducted on 75 person with age from 15- above 60 years, distributed into three groups. The first group included HL patients , while the second group included NHL patients and the control (third) group, the study carried out over a period of 6 months from 20- October 2021 to 29-April 2022, and conducted at Hematology Center in Baghdad Teaching Hospital / Baghdad Medical

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City with a 250-bed capacity and AlKaadimeya Medical City with a 50-bed capacity and Radiology Department / Al Yarmook Teaching Hospital all of centers in the capital Baghdad in Iraq.

Study Population

The study population included 25 patients (11 male and 14 female) with HL with 45 lymphomatous CLN and 25 patients (15 male and 10 female) with NHL with 47 lymphomatous CLN, both diagnosed according to histopathology and immunephenotyping, both groups associated with cervical lymphadenopathy, those patients were examined pre chemo and radiotherapy, Inclusion criteria for lymphomatous CLN were (Absence of fatty hilum, Minimum transverse diameter of 10 mm or larger, Round shape, Echo reticulation, Hypoechoic echogenicity), and 29 normal CLN 25 (13 male and 12 female) healthy control group with no history of neck surgery, glandular fever, chronic tonsillitis, tuberculosis, head and neck malignancy, or lymphomas, inclusion criteria for normal lymph nodes (oval shape, hypoechoic, with Fatty hilum). Age, sex match with patients groups from 15- >60 years old.

Data Collection Procedures, Study Variables and Definitions

Gray-scale US examination was done by radiologists using Voluson Ultrasound Machine, the ultrasound machine was with multi-frequency (7- 14 MHz) and GE 11L-D Linear Array Probe. Scanning patients was performed while the patient was in the supine position, with the neck of the patient hyperextended with a pad or pillow under the shoulders to provide optimum exposure of the neck, Gray-scale US examination was done by sonologists using Voluson Ultrasound Machine, the ultrasound machine was with multi-frequency (7- 14 MHz) and GE 11L-D Linear Array Probe. Scanning patients was performed while the patient was in the supine position, with the neck of the patient hyperextended with a pad or pillow under the shoulders to provide optimum exposure of the neck. The size and shape index which were considered in this study are as follows:

1. **Long axis (L)**: the largest dimension of the lymph node.
2. **Short axis (S):** the greatest dimension perpendicular to (L).
3. **Shape index (S/L) ratio :** the ratio of **S** to **L**. the nodes were divided into 2 groups as S/L <0.5 (**oval**) and S/L >0.5 (**round**).

Statistical analysis

The comparison of qualitative variables was made through the Contingency Coefficients (C.C.) test for the cause's correlation ship of the contingency tables. One sample Chi-Square test. Levene and one-way ANOVA respectively, (Games-Howell – GH) test and Receiver Operation Characteristic-(ROC)" curve. With statistical package (SPSS) ver. (22.0).

3- Results

Table (1) of Distribution of Demographical Characteristics variables (DCVs), with respect of **gender** studied groups has (NS) different at P>0.05. and this is in fact due to the different distribution of patients in HL group, which recorded an increase in female patients, while male patients were the highest registered with the others groups, **age** group's distribution of the studied groups has a (HS) different at P<0.01, and accordance with this result, early ages of patients were recorded in HL group, especially at the first and second age groups, means and deviations of the studied groups (Control, NHL, and HL) were recorded (37.69 ± 12.67), (47.92 ± 14.91), and (28.84 ± 11.05) years respectively.

Table (1): Distribution of DCVs for the studied NHL, HL and control group with testing significant.

DCV.	**Diagnosis**	**Control**		**NHL**		**HL**		**C.S. (*) P-value**
	Classes	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Gender	**Male**	**13**	**52**	**15**	**60**	**11**	**44**	**CC= 0.196 P=0.157 (NS)**
	Female	**12**	**48**	**10**	**40**	**14**	**56**	
	Total	**25**	**100**	**25**	**100**	**25**	**100**	
Age Groups	**< 20**	**1**	**4**	**1**	**4**	**7**	**28**	**CC= 0.522**

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Yrs.	**20 _**	**7**	**28**	**2**	**8**	**9**	**36**	**P=0.002 HS**
	30 _	**6**	**24**	**4**	**16**	**3**	**12**	
	40 _	**5**	**20**	**6**	**24**	**5**	**20**	
	50 _	**4**	**16**	**7**	**28**	**1**	**4**	
	60 _ 70	**2**	**8**	**5**	**20**	**0.00**	**0.00**	
Mean ± SD		**37.69 ± 12.67**		**47.92 ± 14.91**		**28.84 ± 11.05**		

HS: Highly Sig. at P<0.01; S: Sig. at P<0.05; NS: Non Sig. at P>0.05; Testing are based on a Contingency Coefficient test.

Table (2) distribution of lymphomatous CLN in HL, NHL groups and normal CLN in control group, and results showed that shows on significant relation at P>0.05, which indicates the similarity of the selection of lymph nodes in different sites on all the groups studied.

Table(2): distribution of lymphomatous CLN in HL, NHL groups and normal CLN in control group.

Lymph Node Shape and Sites	Control		Non Hodgkin Lymphoma		Hodgkin Lymphoma		C.S. (*) P-value
	No.	%	No.	%	No.	%	
Parotid	4	13.8	3	6.4	5	11.1	CC=0.355 P= 0.359 NS
Sub Mental	4	13.8	1	2.1	1	2.2	
Sub Mandibular	6	20.7	9	19.1	6	13.3	
Upper Cervical	0	0.00	6	12.8	6	13.3	
Middle Cervical	5	17.2	8	17.0	5	11.1	
Lower Cervical	2	6.9	4	8.5	4	8.9	
Left Supraclavicular	6	20.7	10	21.3	8	17.8	
Right Supraclavicular	1	3.4	5	10.6	5	11.1	
Posterior Triangle	1	3.4	1	2.1	5	11.1	
Total	29	100	47	100	45	100	

S: Sig. at P<0.05; NS: Non Sig. at P>0.05; Testing are based on a Contingency Coefficient test

Table (3) shows means of CLN measurements (L) , (S) and S/L for study groups. Results showed that HL group has recorded the high level of CLN (L) and (S) measurements with means of (23 mm) and (13.59 mm) respectively; S/L was (0.634mm). mean of (L), (S) short measurements for NHL group were (21.47, 13.23) mm respectively and S/L ratio was (0.601mm), While for control group were (9.08, 3.85) mm respectively and S/L ratio was (0.424mm).

Table (3): Axis measurements (Long , Short) and Short/Long ratios for studied groups.

Lymph Node Shape	Groups	No.	Mean	Std. D.	Std. E.	95% C.I. for Mean		Min.	Max.
						L.b.	U.b.		
Long	Control	29	9.08	2.86	0.53	7.99	10.17	5.3	18.2
	NHL	47	21.47	9.13	1.33	18.79	24.15	9	42
	HL	45	23.00	8.51	1.27	20.44	25.56	7.2	49
Short	Control	29	3.85	1.39	0.26	3.32	4.38	1.7	7
	NHL	47	13.23	6.83	1.00	11.23	15.23	4.3	30
	HL	45	13.59	5.56	0.83	11.92	15.26	4.1	30.7
Short/Long	Control	29	0.424	0.098	0.018	0.387	0.462	0.244	0.641
	NHL	47	0.634	0.230	0.034	0.567	0.702	0.208	0.986
	HL	45	0.601	0.150	0.022	0.556	0.646	0.333	0.941

According to table (3) readings of CLN (L) and (S) measurements and (S/L) ratio are thrown from the same population, and proved according to testing equal variances are assumed, as well as testing equality of mean vales are assumed by applying "Levene and one-way ANOVA" respectively, and as illustrated in the table (4).

Table (4): Testing equal variances and equal mean values for CLN(Long and Short axis) measurements and (Short / Long axis) ratio in NHL, HL and control groups.

Lymph Node Shape	Testing Homogeneity of Variances		ANOVA- Testing equality of means	
	Levene Statistic	Sig. (*)	F-test	Sig. (*)
Long	12.171	0.000 (HS)	31.396	0.000 (HS)
Short	22.352	0.000 (HS)	33.489	0.000 (HS)
Short/Long	16.272	0.000 (HS)	13.669	0.000 (HS)

(*) HS: Highly Sig. at P<0.01.

According to **table (4)** of testing equal variances and equal mean values are assumed for (L), (S) measurements, results showed that highly significant different are accounted at P<0.01 among studied groups, as well as with (S / L) ratio's mean values estimates.

And according to the obvious results, it needs to be continuing testing of alternative statistical hypothesis which says that at least two groups are not equal due to their mean values, and that should be obtained through applying (Games-Howell – GH) test, which assuming that variances among groups are assumed not equal, in order to allocate in which compromised pairs wised of groups that lymph node size (L), (S) and (S /) ratio readings, are not equal, and as illustrated in **table (5).**

Table (5): Pairs wised comparisons using (GH) test among studied groups for (Long and Short axis) measurements and (Short / Long axis) ratio readings

Lymph Node Shape	(I) Group	(J) Group	Mean Diff. (I-J)	Sig.	C.S. (*)
Long	Control	NHL	-12.387	0.000	HS
		HL	-13.917	0.000	HS
	NHL	HL	-1.530	0.684	NS
Short	Control	NHL	-9.385	0.000	HS
		HL	-9.744	0.000	HS
	NHL	HL	-0.359	0.959	NS
Short/Long	Control	NHL	-0.210	0.000	HS
		HL	-0.177	0.000	HS
	NHL	HL	0.033	0.691	NS

HS: Highly Sig. at P<0.01; Non Sig. at P>0.05; Testing based on GH test.

According to **table (5),** results showed that controlled group are recorded highly significant differences at P<0.01with respect to (NHL, HL) groups, while no significant different at P>0.05 are accounted between NHL, HL groups. Both (L) and (S) and S/L showed good discriminatory value to discriminate between NHL and HL patients from healthy subjects. While, theses parameters were insufficient to discriminate NHL from HL and vice versa.

In table (6). The cutoff points estimated with characteristic-(ROC) curve, as well as a significant levels for testing area under the guideline of 50%, with 95% confidence interval of all probable combinations among a NHL, HL groups in light of studied CLN of mentioned parameter in contrast of a base line (The controlled group), and all probable combinations among HL group in light of studied CLN of mentioned parameter in contrast of a base line (NHL group)

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Table: (5): Receiver Operating Characteristic (ROC) for Cutoff points of (Long and Short Axis) measurements and Short / Long axis ratio in study groups

Axis & Ratio	Base line	Target line	Cutoff Point	Sen.	1- Spe.	Area	P value
Long Axis	Control	NHL	13.85	0.787	0.966	0.938	0.000
		HL	13.85	0.933	0.966	0.957	0.000
	NHL	HL	14.65	0.911	0.255	0.563	0.301
Short Axis	Control	NHL	5.800	0.894	0.931	0.963	0.000
		HL	7.150	0.911	1.000	0.988	0.000
	NHL	HL	8.550	0.844	0.319	0.535	0.563
Ratio S/L	Control	NHL	0.540	0.660	0.862	0.776	0.000
		HL	0.447	0.844	0.724	0.839	0.000
	NHL	HL	0.332	0.989	0.148	0.455	0.458

Null hypothesis: true area = 0.5

The results were : in relation of NHL group (target line) to base line control group (L) cutoff point was 13.85mm with area under the curve (AUC) (0.938), (S) cutoff was (5.8 mm) with AUC value (0.963) and S/L ratio cutoff point (0.540mm) with AUC value (0.776), Figure (1) .

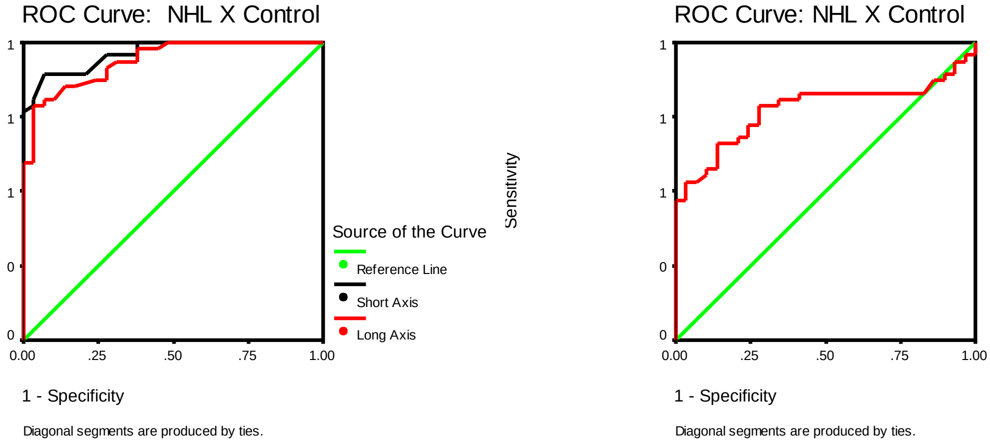

Figure (1): ROC-Curve plots for studied Lymph Node (S), (L) and S/L Outcomes with (Controlled and NHL) group's combinations.

In relation of HL group (target line) to base line control group (L) cutoff point was 13.85mm with area under the curve (AUC) (0.957), (S) cutoff was (7.15mm) with AUC value (0.988) and S/L ratio cutoff point (0.447mm) with AUC value (0.839), Figure (2) .

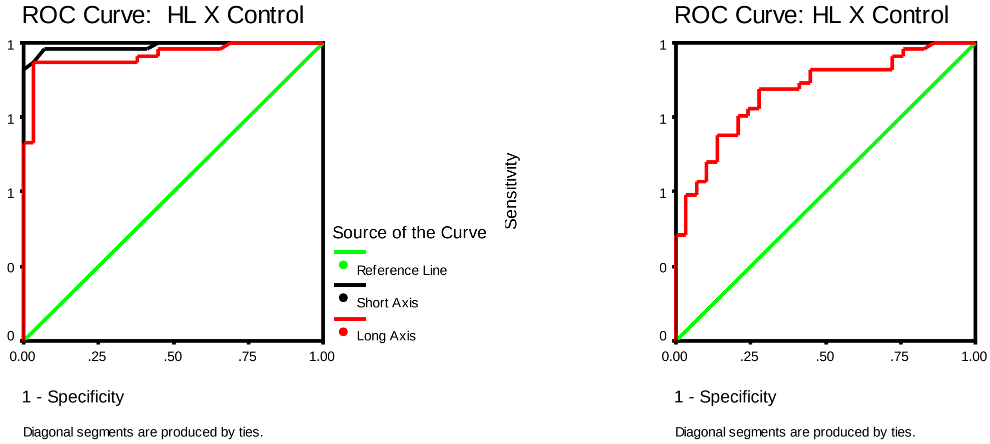

Figure (2): ROC-Curve plots for studied Lymph Node (S), (L) and S/L Outcomes with (Controlled and HL) group's combinations.

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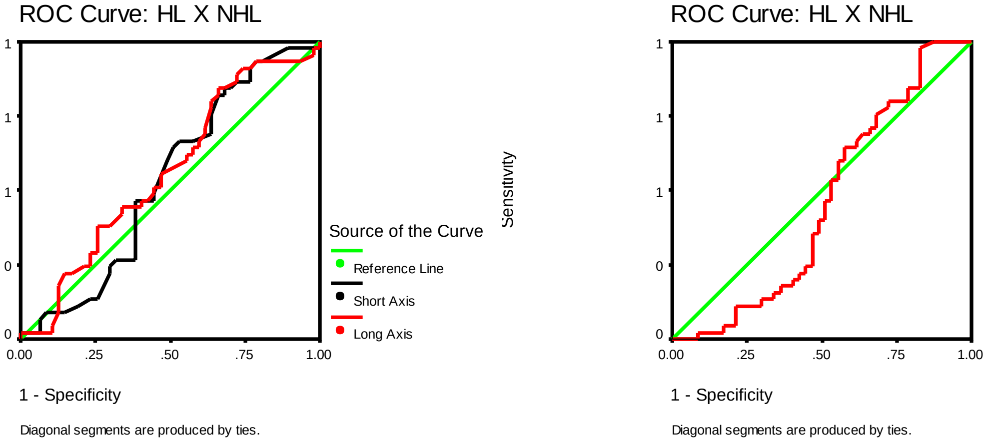
In relation of HL group (target line) to base line NHL group (L) cutoff point was 14.65mm with (AUC) (0.563), (S) cutoff was (8.550mm) with AUC value (0.535) and S/L ratio cutoff point (0.332mm) with AUC value (0.455), Figure (3) .



Figure(3): ROC-Curve plots for studied Lymph Node (S), (L) and S/L Outcomes with (NHL and HL) group's combinations.

At P<0.01 regarding of NHL, HL groups, which were adopted by the controlled group (The base line with second category cases indicators), the results of the diagnostic strength were in the favor of the mentioned cutoff points.

With respect to HL group, results shows that no significant of area are recorded by "NHL" group, which was adopted as (The base line), there was no significant relation at at P>0.05, it is worth noting that despite the slight differences between S/L of (NHL, HL) groups.

4. DISCUSSION

Long (L) and Short (S) Axis} measurements, { Short / Long axis(S/L)} ratio and their Cutoff Points among NHL, HL and control group : The size of lymph nodes is measured by two axis: the short axis (S) and the long axis (L), the shape index of lymph nodes is usually evaluated by the S/L ratio *Osanai et al*[5]. *Tohnosu et al* [6] stated that lymph nodes with a (L) diameter >10 mm and with S/L > 0.5mm exhibited a much higher incidence of malignancy.

The size of lymphomatous lymph nodes varies significantly, although lymphomatous nodes tend to be enlarged with a minimum transverse diameter (short axis) of 10 mm or larger, nodal size alone is not an accurate criterion for differentiating lymphomatous lymph nodes from normal or other pathologic lymph nodes *A.T. Ahujaa [A] et al* [7], while *Craig ,Brooke and Lewis* [8] mentioned that the transverse diameter (short axis) varies according to site of CLN, in the submandibular region (6mm), in the submental and posterior triangle regions the maximal transverse diameter was approximately (3mm), the upper cervical and parotid nodes were approximately (5mm) and (4mm) respectively, whereas the middle cervical nodes were found to be the smallest (2mm) and Defining the upper size limit of a normal lymph node remains controversial.

M. Ying et al [3] mentioned that there is no agreement on which cut-off point should be used in routine clinical practice, and they mentioned that *Van den Brekel et al; 1992* noted that the optimal cut-off point of nodal size varies with the patient population, and they suggested that for any patient population the most acceptable size criterion is 9 mm for deep cervical nodes and 8 mm for other cervical lymph nodes, while *Imani et al*[9] used 7 mm and 13 mm as cutoffs for minimal and maximal nodal diameter, respectively. *Rohan et al*[10] mentioned that they found an S/L cut-off of 0.595mm in previous studies with a sensitivity, specificity and accuracy of 79.3%, 74.7% and 77.1%, respectively, also they mentioned that (S) cut off of 8mm for all CLN was used the accuracy 85%.

The results regarding Long (L) and Short (S) Axis} measurements : HL group presented with short axis with minimum and maximum readings (4.1mm), (30.7mm) respectively, with mean of (13.59mm), this agree with [7] , [8] and *Prinson and Aria* [11]. NHL group presented with (13.23mm) mean of short axis with minimum and maximum readings (4.3 mm), (30 mm) respectively, also agree with [7] , [8] and [11].

Control group presented with (3.83) mm mean short axis with minimum and maximum readings 1.7 mm, 7 mm respectively, and these results on line with *Ying and Ahuja* [12], *Joe, Lewis and R. Brooke*[13] and *Rand, Ammar and Mohammad*[14].

Hodgkin's lymphoma group has recorded mean of (23mm) long axis with minimum and maximum readings (7.2mm), (49mm) respectively, these result agree with *Shahad, Taghreed and Mohammed* [15] and *Chae et al* [16].

Non Hodgkin's lymphoma group present with mean (21.47mm) long axis with minimum and maximum readings (9mm), (42 mm) respectively, the results less than that obtained with [14] and [16], while *Abhishek et al* [17] in their study on (34) lymphomatous CLN in NHL and HL as the mean was (15.2mm) and the apposite in the result of *Mohamed, Tamer and Haney* [18] in their study on 12 patients with NHL HL result of was mean (35mm).

Control group presented with mean of (9.08mm) long axis with minimum and maximum readings (5.3mm), (18.2mm) respectively, the result agree with [14] **and** *Okumuş, Dönmez and Pekiner* [19].

A large gap of nodal size between NHL, HL groups and control group regarding (S) and (L), while no significant relation within NHL and HL groups, that seems to be nodal size highly significant indicator to differentiate between normal and lymphomatous lymph node, while there were no significant difference between NHL, HL groups.

(Short / Long axis) Ratio : Results showed that (NHL, HL) groups has recorded the high level of (Short/Long axis) ratio's mean values estimates (0.634mm) and (0.601), and maximum mean of (0.986mm), (0.941mm) respectively, and they are accounted more than cutoff point (0.5mm), while it is noted that there is a large gap of controlled estimates with mean of (0.424 mm) , and it accounted mean value estimate less than a cutoff point with minimum and maximum mean (0.244mm), (0.641mm) respectively, so there was high significant relationship regarding (Short/Long axis) ratio's between both NHL, HL groups and control group.

Cutoff points : The results were highly significant of area are recorded by (L) and (S) measurements, at $P<0.01$ regarding of NHL, HL groups, which were adopted by the controlled group (The base line), The results were of the diagnostic strength.

With no significant of area are recorded by "NHL" group at $P>0.05$, which was adopted as (The base line) to HL (target line) , so there was no significance for differentiate between NHL and HL with (S) and (L).

Short / long axis ratio : Results showed that highly significant of area are recorded by S/L , at $P<0.01$ regarding of NHL, HL groups, which were adopted by the controlled group (The base line with second category cases indicators), the results of the diagnostic strength were in the favor of the mentioned properties.

With no significant of area are recorded by "NHL" group at $P>0.05$, which was adopted as (The base line) to HL (target line) , so there was no significance for differentiate between NHL and HL with S/L .

5. Conclusion

gray-scale US sonographic parameters { (L), (S), S/L} cutoff points were of diagnostic strength in differentiating between lymphomatous CLN in NHL, HL groups and normal CLN in healthy control group, that more than cutoff points values (13.85, 5.800, 0.540)mm predict occurrence of NHL and (13.85, 7.150, 0.447)mm predict occurrence HL , while there were no significant differences between NHL, HL groups regarding studied parameters.

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