Frontiers in Health Informatics ISSN-Online:2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 3
Open Access

Comparison of 'Fascin' Expression in Various Subtypes of Lymphoproliferative Disorders

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Cite this paper as: Mrs. Swati Sharma, Dr. Anuradha Kusum, Dr. Mansi Kala, Mr. Randhir Kumar Mahato (2024). Comparison of 'Fascin' Expression in Various Subtypes of Lymphoproliferative Disorders. *Frontiers in Health Informatics*, *13 (3) 9369-9386*

Abstract

Lymphomas, a diverse group of lymphoproliferative disorders, present diagnostic challenges. Fascin, a dendritic cell marker, helps identify Reed-Sternberg cells in Classical Hodgkin's Lymphoma (CHL) and is also present in some Anaplastic large-cell Lymphomas (ALCL) and Diffuse Large B-Cell Lymphomas (DLBCL). This study at Swami Rama Himalayan University analyzed Fascin expression in 63 lymphoma cases using histopathological and immunohistochemical techniques. B-cell NHL types other than DLBCL and patients with T cell/histiocyte-rich large B-cell Lymphoma (THRBCL) undergoing chemotherapy were excluded. Results showed Fascin positivity in 100% of Nodular Lymphocyte Predominant HL (NLPHL) and Nodular Sclerosis CHL (NSCHL), 90% in Mixed Cellularity CHL (MCCHL), 50% in Lymphocyte Rich CHL (LRCHL), 6% in DLBCL, 50% in THRBCL, and 80% in ALCL. While Fascin is useful for some Hodgkin's lymphoma subtypes, it cannot differentiate between HL and NHL alone. Further research with additional markers and larger sample sizes is necessary to understand why certain subtypes express Fascin at higher levels, potentially uncovering new insights to enhance diagnostic and therapeutic strategies.

Keywords: *Fascin, Lymphoproliferative disorders, Lymphoma, Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma, Anaplastic large cell Lymphomas*

Introduction

Fascins are a family of actin-bundling proteins, crucial for organizing actin cytoskeleton in various cell types. It includes proteins from sea urchins, HeLa cells, and Drosophila. Fascin is conserved across many species, but not found in yeast. Sea urchin Fascin shares 35% amino acid identity with the Drosophila singed protein. Fascins from humans, mice, and Xenopus are similar to each other but distinct from other actin-bundling proteins like villin and fimbrin. Fascin bundle F-actin (filamentous actin) in vitro and are localized in various cell structures. Sea urchin Fascin is involved in forming filopodia in coelomocytes and microvillar cores during fertilization. Human Fascin is found in filopodia, membrane ruffles, stress fibers and microspikes in different cell kinds. Fascin is highly prevalent in brain, spleen, neuronal and glial cells, microcapillary endothelial cells, and dendritic cells. These cells typically have many membrane protrusions, indicating Fascin's role in membrane extension and cell motility. Many transformed cells exhibit high levels of Fascin, such as virus-transformed fibroblasts, HeLa cells, and Epstein-Barr virus-infected B lymphocytes. These cells show changes in shape, motility, and loss of cell-cell contacts, all linked to alterations in the actin cytoskeleton. Transformed cells with high Fascin levels exhibit increased membrane extensions, highlighting Fascin's involvement in these structures.LLC- PK1 pig epithelial cells naturally have low Fascin levels, making them suitable for studying the effects of exogenous Fascin expression. Clones expressing human Fascin show numerous surface extensions, such as micro spikes and lamellipodia leading to increased cell motility. Fascin transfectants have 8-17 times higher migration activity compared to parental cells, as measured by a modified Boyden chamber. Microinjection of Fascin protein induces membrane extensions, directly linking Fascin to the reorganization of the peripheral actin cytoskeleton. (1)

It has been revealed through immunohistochemical research that the dendritic cells within lymphatic tissues can be specifically identified by utilizing a monoclonal antibody (mAb) Fascin that targets them. (2) Earlier research indicated that Fascin expression in germinal center dendritic cells is modified in neoplastic follicles of follicular lymphomas and within the reactive follicular hyperplasia. (3) The Hodgkin lymphoma cell lineage KM-H2 exhibited characteristics of both dendritic and B cells. (4) Further researchers identified that Reed-Sternberg (RS) cells and their variants within classical Hodgkin lymphoma (CHL) consistently tested positive for Fascin whereas, lymphocytic and histiocytic cells in nodular

lymphocyte-predominant Hodgkin lymphoma did not express Fascin. All the findings suggest that Fascin could be a specific marker for RS cells. (5)

Additionally, LMP1, a crucial protein in Epstein-Barr virus (EBV), contributes to cancer development by mimicking the CD40 receptor and activating various signaling pathways. These pathways lead to changes in cell behavior, such as increased Fascin expression, which enhances the invasive and migratory properties of cancer cells. Understanding these mechanisms is vital for developing targeted treatments for EBV-associated cancers. (6)

Researchers have observed Fascin expression within Hodgkin's lymphomas, various subtypes of non-Hodgkin's lymphomas, and cancers outside the lymphoid category. Many researches show Fascin is either minimally expressed or absent in epithelial cells of different organs, but is markedly elevated across a range of epithelial neoplasms (such as carcinomas of the esophagus, lung, cervix, ovary, stomach, pancreas, larynx, liver, colon, breast, and nasopharynx), where it correlates with more aggressive behavior and a worse prognosis. (7–11)

While Fascin is a marker for progression and violent behavior in epithelial cancers, it serves as a dependable marker for distinguishing Hodgkin's lymphoma with different types of non-Hodgkin's lymphomas. Research indicates that nearly each Reed-Sternberg cell in Hodgkin's lymphoma strongly exhibits Fascin, making it a valuable immunohistochemical marker for differentiating Hodgkin's from non-Hodgkin's lymphomas, including DLBCL and ALCL. (12,13)

This study aimed to evaluate the effectiveness of Fascin as a biomarker for distinguishing classical Hodgkin's lymphoma from different non-Hodgkin's lymphomas in complicated cases.

Material &Methods

Tissue specimens, routinely processed and paraffin-embedded after formalin fixation, were retrieved from the archives of the Pathology Department, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, Uttarakhand from year 2019-2023. All confirmed cases with Classical Hodgkin's Lymphoma, Nodular lymphocyte predominant Hodgkin's lymphoma, T- NHL and B-NHL were part of this study. Cases with low grade NHL, relapsed cases and samples post chemotherapy were excluded from the study. All tissues were fixed in 10% formalin. Total 63 cases of Lymphoma comprising both Hodgkin's

Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL) were included in the study. The HL group included 33 cases, of which 9 were Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL) and 24 were Classical Hodgkin's Lymphoma (CHL). The CHL cases comprised 5 of Nodular Sclerosis Classical Hodgkin's Lymphoma (NSCHL), 8 of Lymphocyte Rich Classical Hodgkin's Lymphoma (LRCHL), and 11 of Mixed Cellularity Classical Hodgkin's Lymphoma (MCCHL). The NHL group consisted of 30 cases, of which 18 were B-NHL and 12 were T-NHL. Among the 18 B-NHL cases, 16 were of Diffuse Large B cell Lymphoma (DLBCL) and 2 were of T cell Rich B cell Lymphoma (THRBCL). Of the 12 T-NHL, 2 were T- Cell Lymphoblastic Lymphoma (T-LBL), 4 were Peripheral T cell Lymphoma (PTCL), 5 were Anaplastic Large Cell Lymphoma (ALCL), and 1 was Angioimmunoblastic Lymphoma (AITL). Among 63 cases, the DLBCL were the most i.e. 25%. Figure.1: illustrates the distribution and frequency of Lymphoma types included in the study.

In all cases, diagnoses were made following standard procedures, which included morphological examination, and immunohistochemical analysis. Initially, Hematoxylin and Eosin (H&E) staining was performed on formalin-fixed, paraffin-embedded tissue blocks to confirm the morphological characteristics of the lymphoma. The IHC analysis was conducted on 63 representative tissue samples using Fascin-1, a primary antibody. Following deparaffinization, the sections were processed employing an avidin-biotin complex detection system, preceded by heat-mediated epitope retrieval in a 10mM citrate buffer (pH 6.0) followed by antibody binding and chromogen detection. The staining utilized a mouse anti- human Fascin monoclonal antibody, Fascin-1- (Mob 560, PDM560) (Diagnostic Biosystems) clone 55K-2, an IgG1 immunoglobulin.

Experiments included both positive and negative controls. Positive staining was defined as at least 10% of the target cells showing cytoplasmic reactivity. Sections with excessive background staining were removed from the analysis. Results obtained were classified as negative, mildly positive, or intensely positive. Fascin reactivity levels were assessed among various Lymphoma types. The immunostaining was carried out independently by two investigators, with any discrepancies resolved through a joint review. Positive (ovary dendritic cells) and negative (appendix) controls were included for accuracy. Strong staining in interdigitating dendritic cells was utilized as an internal control for reference. Staining intensity was classified using a three-level scale: strong positive (comparable to or similar to

interdigitating dendritic cells), weak positive staining (less intense than interdigitating dendritic cells) and negative (no staining).

Consent was obtained from all participants, with every patient providing written agreement. This study was authorized by the Institutional Ethics Committee before initiation, under approval number SRHU/HIMS/ETHICS/2022/148. All protocols followed the ethical standards established by the Institutional Ethical Committee, the 1964 Helsinki Declaration with its subsequent amendments, or equivalent ethical guidelines. No animal-related research was included in this article.

Statistical analysis:

For statistical analysis, Pearson's chi-square test was employed to assess differences in Fascin levels among NLPHL, CHL, DLBCL, ALCL and other Lymphoma subtypes, utilizing SPSS software, version 11.0 (SPSS, Chicago, IL).

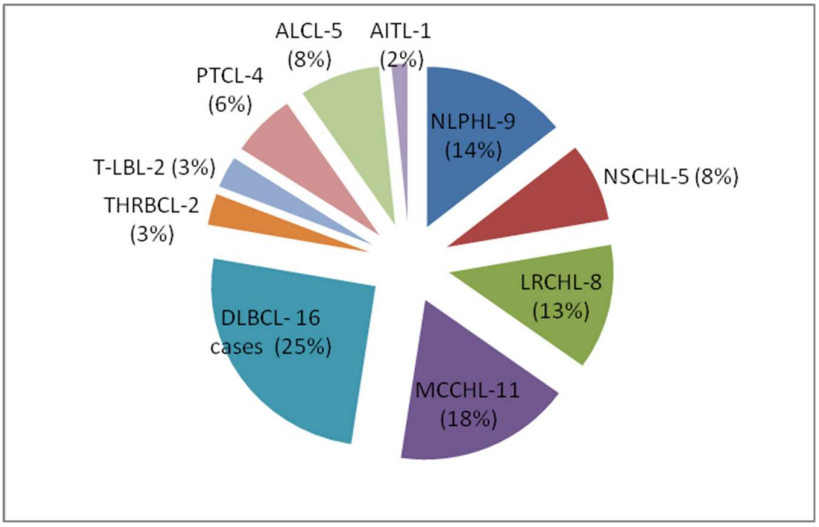


Figure.1: Distribution and Frequency of Lymphoma types included in this study

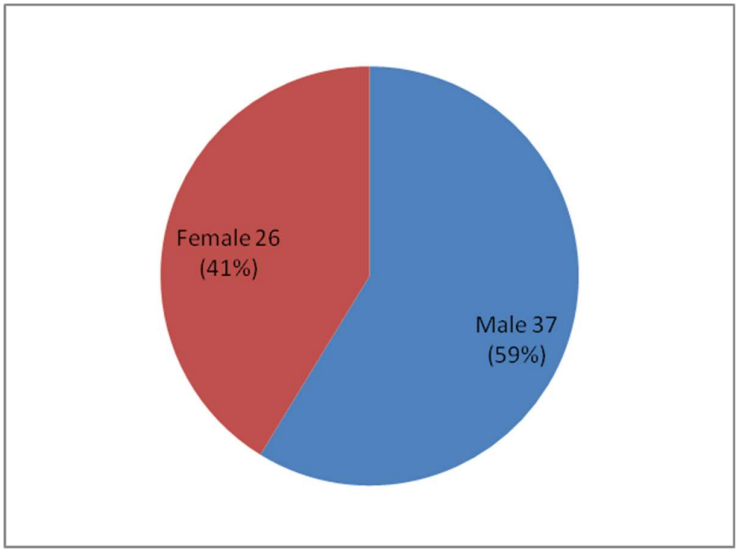


Figure.2: Participant's Gender Distribution

Table.1: Participant's Age Distribution in groups

S.No.	Age Groups	Nos.
1	1-20 years	12
2	21-40 Years	18
3	41-60 years	17
4	61-80 years	16

Results:

Different age groups, encompassing both males and females were included with average age of 43.3 years, median age of 44 years, the standard deviation of 22.67 years. The gender distribution included 37 (59%) males and 26 (41%) females. Figure.2 depicts the participant's gender distribution. Table.1 depicts the participant's age distribution in groups. Most patients were with one or more enlarged lymph nodes in the neck, armpit or groin. Systemic B symptoms, lymphadenopathy, splenomegaly, mild anemia was more common in patients. Out of total 63 Lymphoma cases, in 33 Hodgkin's Lymphoma cases- NLPHL and NSCHL both exhibit a 100% positive expression rate of Fascin, with 9 and 5 cases respectively. LRCHL shows a 50% positive expression in 8 cases, while MCCHL has a 90% positivity rate in 11 cases. Out of total 33 cases of HL 28 cases were found positive with Fascin. Moving to 30 cases of Non-Hodgkin's Lymphoma, that comprises 18 cases of BNHL and 12 cases of TNHL. Among 18 cases of BNHL, DLBCL showed a low Fascin positivity rate of 6% out of

16 cases, THRBCL reports a 50% positive expression in 2 cases. Out of total 18 cases of BNHL, the positivity was found only in 2 cases. Among 12 cases of TNHL, Both T-LBL and PTCL show no positive expression in 2 and 4 cases respectively. ALCL displays an 80% positive expression in 5 cases, whereas AITL has no positive expression in its single case. Out of total 12 NHL, only 4 were found positive. Figure.3 depicts Fascin expression in various subtypes of Lymphoma, Figure.4 depicts IHC Fascin staining results for NLPHL, MCCHL, DLBCL, ALCL. These results underscore the differential expression patterns of Fascin across various NHL subtypes. The statistical test employed to assess these differences was Pearson's Chi-square test**,** a widely used method for analyzing associations between categorical variables, in this case, lymphoma subtypes and Fascin expression levels. The obtained p-value, which is less than 0.0001, indicates a highly notable difference in Fascin staining among the lymphoma subtypes, including CHL, DLBCL, ALCL and others. This underscores the differential Fascin expression patterns across various lymphoma subtypes.

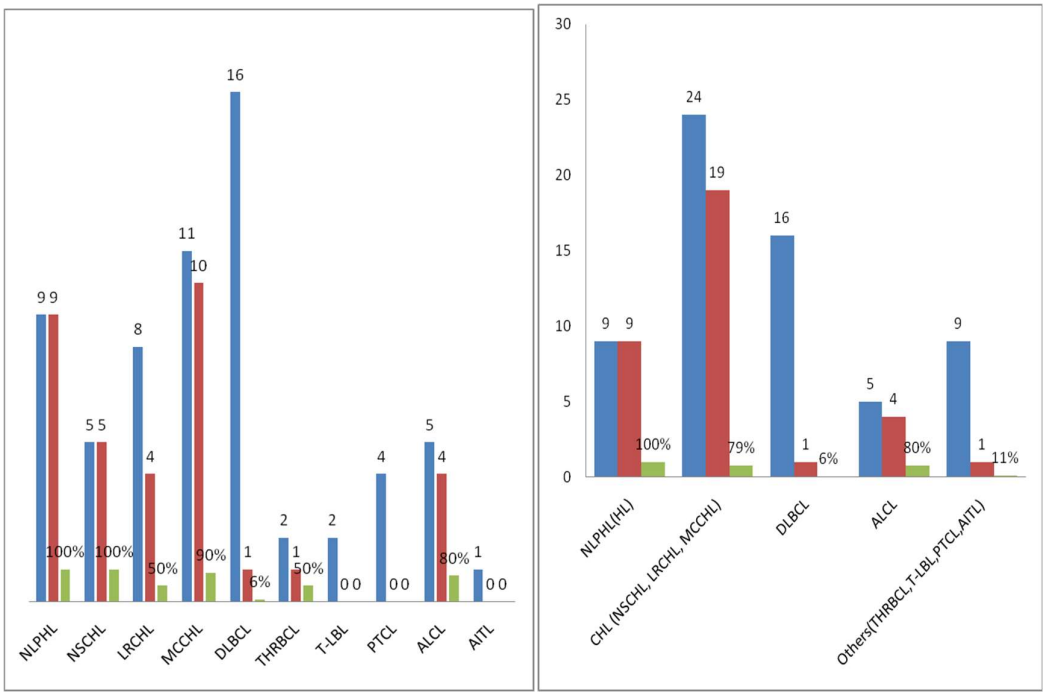
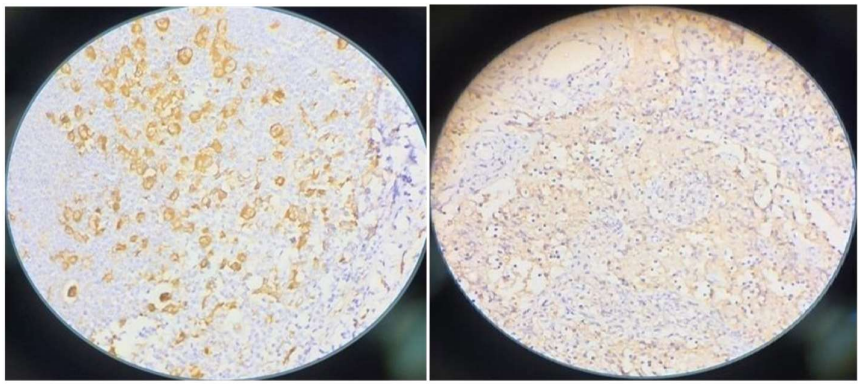
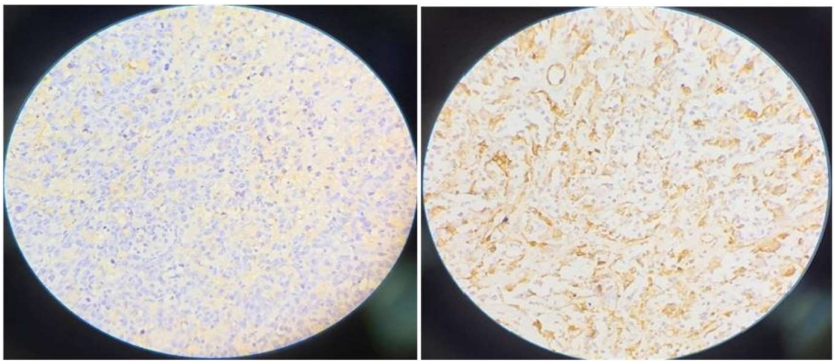


Figure.3: Fascin expression (Pos%) in various subtypes of Lymphoma (Total 63 cases (HL, CHL 33 &NHL 30))



A. NLPHL B. MCCHL



C. DLBCL D. ALCL

Figure.4: IHC Fascin staining results for Nodular Lymphocyte Predominate HL (NLPHL), Mixed Cellularity CHL (MCCHL), Diffuse Large B Cell Lymphoma (DLBCL), Anaplastic large cell Lymphoma (ALCL). A. NLPHL, B. MCCHL, C. DLBCL, D. ALCL

Discussion

This study is a hospital-based cross-sectional descriptive analysis performed over a 5-year period (2019-2023) at the SRHU hospital. All age group (1 to <80 years) cases with confirmed Classical Hodgkin's Lymphoma, Nodular lymphocyte predominant Hodgkin's lymphoma, T-NHL and B-NHL were taken up for this study from the year 2019-2023. 63 individuals in the hospital were selected. Different age groups encompassing both males and females with mean age of 43.3 years and median age of 44 years were included, indicating that half of the participants were younger than 44 and half were older. The standard deviation of 22.67 years reflects a wide variability in ages among the participants. The gender

distribution included 37 (59%) males and 26 (41%) females indicate that male subjects are more affected with Lymphoma than females.

Different studies on the utility of Fascin as a marker for differentiating Hodgkin lymphoma (HL) from different types in non-Hodgkin lymphoma (NHL) reveal subtle variations. Our investigation into Fascin expression across various subtypes of HL and NHL has also revealed nuanced patterns that contribute to our understanding of the molecular landscape in these hematological malignancies.

A study by Pinkus et al. found that nearly every Hodgkin's disease (HD) case except Nodular Lymphocyte Predominant HL (NLPHL) were Fascin-positive, with only 15% of non-Hodgkin's lymphomas (NHL) showing reactivity. In contrast, the current study of 63 lymphoma cases reveals that 100% of NLPHL and NSCHL cases are Fascin-positive, along with 90% of mixed cellularity classical HL (MCCHL) and 50% of lymphocyte-rich classical HL (LRCHL). For NHL, only 11% B-cell NHL and 33% T-cell NHL cases were Fascin-positive. These results confirm Fascin's effectiveness in marking most HD cases and its limited reactivity in NHL.(14)

Another study by Fan et al. investigated Fascin expression frequency in 30 cases of Anaplastic large cell lymphoma and 34 classical Hodgkin’s disease and its clinical usefulness in correlation with CD30 and ALK-1(Anaplastic lymphoma kinase) staining impressions. Result showed that Fascin was strongly positive in all classical Hodgkin's disease (HD) cases and most anaplastic large cell lymphoma (ALCL) cases, although positive staining did not differentiate between ALCL and HD. Negative Fascin results effectively ruled out classical HD, suggesting its utility in complex diagnostic cases of ALCL and HD. This study concludes strong positivity of Fascin in classical HD and majority of ALCLs. The present study aligns with this study in strong Fascin expression in HL, particularly in NSCHL and MCCHL. ALCL shows 80% positivity in the current study, consistent with the majority positivity reported by Fan et al.(3)

Fascin expression studied by Bakshi et al. in 41 patients with Diffuse large B-cell lymphoma, 30 patients with Anaplastic large cell lymphoma and 30 patients of CHL in conjunction with ALK-1 expression in ALCL. Bakshi et al. found high Fascin positivity in classical Hodgkin lymphoma (CHL), and it was more effective in differentiating CHL against Diffuse large B-cell lymphoma (DLBCL) than from ALCL. Current study supports this with high positivity

in NLPHL, NSCHL, and MCCHL. Current study shows 80% positivity in ALCL cases, indicating substantial expression but not necessarily diagnostic differentiation.(15)

Fascin and JunB utility were evaluated by Bhargava et al to differentiate Nodular Lymphocyte predominant HL and Lymphocyte rich classical Hodgkin lymphoma on 35 archrival cases of 24 NLPHL and 11 LRCHL. Results provided a basic alternative to other antibody profiles. Current study shows 100% positivity in NLPHL and 50% in LRCHL, which aligns with the difficulty in distinguishing between these subtypes based on Fascin alone. (16)

Another research at Aga Khan University, Idrees et al. investigated 46 patients of Classical Hodgkin lymphomas, 26 patients of DLBCL, 13 patients of ALCL, 8 patients of Peripheral T cell Lymphoma and 2 patients of Angioimmunoblastic Lymphoma. Results showed 100% negative predictive value of Fascin in differentiating Classical Hodgkin Lymphoma with several NHL. Further study was suggested with a greater sample size. Present study also shows significant positivity in HL subtypes but low positivity in most NHL subtypes, supporting Fascin's negative predictive value in NHL diagnosis.(17)

A study at Baskent University conducted by Kocer et al on 55 patients of DLBCL patients treated with R-CHOP therapy found no prognostic significance for Fascin expression, emphasizing the challenge of differentiating classical Hodgkin lymphoma from ALCL and calling for more research into Fascin's clinical relevance, especially concerning specific lymphoma therapies. In current study a very low positivity rate (6%) in DLBCL, indicates limited diagnostic or prognostic utility in this subtype. (18)

The subsequent Table.2: provides a comprehensive comparison of Fascin reactivity across various lymphoma subtypes, highlighting findings from both previous studies and the current research.

Table.2: A comprehensive comparison of Fascin reactivity across various lymphoma subtypes between previous studies and the current research.

		HL	CHL					BNHL	BNHL	TNHL	TNHL	TNHL	TNHL
		NLPHL	NSCHL	LRCHL	MCCHL	LDHL	Unclassified	DLBCL	THRBCL	T-LBL	PTCL	ALCL	AITL
1.	Pinkus et al. (1997)	0/14	132/132	-	34/34	2/2	5/5	-	-	-	-	-	-
	Fascin expression (%)	100 %Neg	100%	-	100%	100%	100%	-	-	-	-	-	-
2.	Fan et al. (2003)	-	29/29	-	5/5	-	-	-	-	-	-	20/30	-
	Fascin expression (%)	-	100%	-	100%	-	-	-	-	-	-	67%	-
3.	Bakshi et al. (2007)	-	19/19	3/3	7/7	-	1/1	6/41	-	-	-	15/30	-
	Fascin expression (%)	-	100%	100%	100%	-	100%	14.6%	-	-	-	50%	-
4.	Bhargava et al. (2010)	-	3/24	11/11	-	-	-	-	-	-	-	-	-
	Fascin expression (%)	-	12.5%	100%	-	-	-	-	-	-	-	-	-
5.	Idrees et al. (2010)	-	21/21	-	22/22	-	-	8/26	-	-	2/8	6/13	0/2
	Fascin expression (%)	-	100%	-	100%	-	-	30.8%	-	-	25%	46.1%	100%Neg
6.	Kocer et al. (2013)	-	-	-	-	-	-	34/55	-	-	-	-	-
	Fascin expression (%)	-	-	-	-	-	-	61.8%	-	-	-	-	-
7.	Present study	9/9	5/5	4/8	10/11	-	-	1/16	1/2	0/2	0/4	4/5	0/1
	Fascin expression	100%	100%	50%	90%	-	-	6%	50%	100%Neg	100%Neg	80%	100%Neg

This study confirms that Fascin expression is consistently high in various subtypes of Hodgkin's lymphoma (HL), including Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL), Nodular Sclerosis Classical Hodgkin Lymphoma (NSCHL), and Mixed Cellularity Classical Hodgkin Lymphoma (MCCHL). This aligns with previous research. However, Lymphocyte Rich Classical Hodgkin Lymphoma (LRCHL) shows variable Fascin expression (50%), reflecting ongoing challenges in differentiation. In non-Hodgkin's lymphoma (NHL), Fascin expression is found generally low within most B-Cell NHL subtypes, particularly Diffuse Large B-Cell Lymphoma (DLBCL), confirming past

findings of limited diagnostic utility in B-Cell NHLs. Conversely, Anaplastic Large Cell Lymphoma (ALCL) exhibits persistently, high Fascin positivity (80%), consistent with previous studies. The absence of Fascin in T-Lymphoblastic Lymphoma (T-LBL), Peripheral T-Cell Lymphoma (PTCL), and Angioimmunoblastic T-Cell Lymphoma (AITL) suggests minimal utility in these T-Cell NHL subtypes. Obtained p-value (0.000) is extremely significant which indicates that the expression levels of Fascin are not uniformly distributed across the different types of lymphomas studied. There is a strong association between the type of lymphoma and the level of Fascin expression, with certain lymphoma types e.g. NLPHL, CHL and ALCL, showing much higher Fascin expression compared to others (e.g., DLBCL).

Conclusion

Study provides deep insights into the varied expression of Fascin in different subtypes of HL and NHL. The consistent Fascin positivity in specific subtypes such as NLPHL, NSCHL and ALCL suggests a potential role for Fascin as a diagnostic marker in these contexts. The diversity in Fascin expression patterns in other subtypes including its low prevalence in DLBCL and variable expression in THRBCL underscores the importance of considering molecular heterogeneity in Lymphoma diagnosis.

Our findings reveal that Fascin expression patterns are complex and vary significantly among different lymphoma subtypes. While Fascin proves useful for distinguishing certain Hodgkin's lymphoma subtypes, it is not effective as a standalone marker for differentiating between Hodgkin and Non-Hodgkin lymphomas overall. Clinically, Fascin serves as a valuable marker for specific Hodgkin's lymphoma subtypes but has limited utility for most non-Hodgkin's lymphoma subtypes.

The inconsistency in Fascin expression highlights the necessity for more extensive research, encompassing studies with larger cohorts and additional biomarkers, to elucidate why specific lymphoma subtypes exhibit higher levels of Fascin. This could offer new insights into the pathophysiology of these diseases. These findings could assist clinicians in enhancing diagnostic techniques and formulating personalized treatment plans for patients with Hodgkin's and Non-Hodgkin's lymphomas.

The summary of Lymphoma cases included in the study.

Cases/ Variables	Age (Y)	Gender	Family History /Patient History	Chief Complains	B Symptoms	Lymphadenopathy	Splenomegaly	BM involvement	Histopathology diagnosis on LN	IHC diagnosis on LN excision	Fascin Expression	Peripheral blood findings													
																					DLC (%)				
												Hb(g/dl)	RBC(M/mm3)	TLC(Th./cumm)	PCV(%)	MCV(fl)	MCH(pg)	MCHC (g/dl)	PLT(Th./cumm)	RDW(%)	N	L	E	M	B
Case 1	52	F	None	Swelling right side of Neck	+	+	+	-	CHL	NSCHL	Positive	11.7	5.13	8.2	38.1	74.3	22.8	30.7	202	16.7	77.6	14.2	0.8	7.2	0.2
case 2	60	M	History of pulmonary TB, Chronic smoker	Swelling in Neck	+	+	+	-	HL	NLPHL	Positive	9.36	3.77	8.77	29.2	77.43	24.83	32.07	249	21.16	75.76	10.05	0.34	12.76	1.09
case 3	65	F	History of COPD/ Asthma	Lymphadenopathy, weakness, codition frail	+	+	+	-	HL	LRCHL	Positive	10.15	4.1	8.93	32.75	79.89	24.75	30.98	145	19.83	78.41	7.06	0.98	13.3	0.25
Case 4	15	M	None	Swelling in Neck	+	+	+	-	Poorly Differentiated Malignant tumor	ALCL	Negative	10.4	3.65	6.2	30.5	83.6	28.6	34.2	231	29.5	67.3	17	5.3	9.4	1
Case 5	20	M	Severe Anaemia,Pneumonia	Shortness of breath, Pallor	+	+	+	+	NHL- ALCL	ALCL	Positive	6.24	3.01	5.22	19.11	73.57	24.01	32.64	104	19.73	88.4	10	0	1.2	0.4
Case 6	80	F	None	Swelling in Neck	+	+	+	-	NHL	DLBCL	Negative	12.71	4.41	7.5	38.93	88.24	28.82	32.66	238.8	14.53	68.7	19.41	1.45	9.46	0.98
Case 7	43	M	None	Swelling in the right side of neck	+	+	+	-	Poorly Differentiated Malignant tumor	DLBCL	Negative	14.9	4.35	6.6	44.5	102.2	34.1	33.4	175	13.2	67.7	18.7	1.5	11.7	0.4
Case 8	23	M	None	Swelling in Neck	+	+	+	-	NHL	DLBCL	Negative	9.51	3.49	7.71	29.9	85.74	27.26	31.8	357.6	19.94	83.56	4.09	0.9	10.82	0.63
Case 9	45	M	None	Swelling in Neck	+	+	+	-	Poorly Differentiated Malignant tumor	DLBCL	Negative	11.34	3.99	9.07	35.33	88.6	28.44	32.1	466.9	16.76	70.11	15.24	0.14	13.53	0.98
Case 10	28	F	None	Swelling right side of Neck	+	+	+	-	HL	NSCHL	Positive	10.6	3.74	2.2	31.4	82.4	26.5	33.5	125	23.8	58.3	31.2	1.6	8.7	0.2
Case 11	6	M	None	Swelling right side of Neck	+	+	+	-	CHL	LRCHL	Positive	13.9	5.8	8.9	41.5	71.1	23.8	33.5	369.6	18.6	37.8	42.7	3.4	15.7	0.4
Case 12	53	M	None	Swelling in Neck	+	+	+	-	NHL	DLBCL	Negative	10.9	3.58	2.1	33	92.1	30.4	33	20	15.6	14	82	4	0	0
Case 13	78	M	None	Swelling over right side of face	+	+	+	-	Lymphoma	DLBCL	Negative	10.9	3.62	5.2	32	88.6	30.2	34.1	164	16.2	58	22	6	14	0

Case 14	80	M	None	Swelling over left intraauricular area, local pain,dysphagia	+	+	+	-	NHL	DLBCL	Negative	12.27	4.08	3.61	37.71	92.32	30.03	32.53	140	18.33	38.25	32.8	12.16	15.96	0.83
Case 15	75	F	Pneumonia	Swelling over left post auricular area & cervical area	+	+	+	-	Poorly Differentiated Malignant tumor	DLBCL	Negative	11.5	4.23	8.1	35.1	82.9	27.2	32.8	167	16.6	72.3	10.6	2.5	14.1	0.5
Case 16	44	F	None	Swelling in Neck	+	+	+	-	Poorly Differentiated Malignant tumor	DLBCL	Negative	11.8	4.49	8.51	37.3	83	29.1	33.5	170.5	17.35	60.1	27.5	4	8	0.4
Case 17	10	F	None	Swelling in Neck	+	+	+	+	NHL	T-LBL	Negative	7.9	2.4	1	23.6	98.5	32.9	33.4	100	20	40.3	16.4	12.7	30.3	0.3
Case 18	73	M	None	Swelling in Neck	+	+	+	-	HL	NSCHL	Positive	12.34	4.68	12.05	39.07	87.3	25.34	33.45	348.9	17.31	74	18	3	4	1
Case 19	80	F	None	Swelling in Neck, Multiple lymph nodes	+	+	+	-	Lymphoproliferative Disorder	NLPHL	Positive	9.75	3.7	2.52	29.29	79.16	26.36	33.3	120	16.97	47.81	23.25	11.46	16.34	1.14
Case 20	32	M	None	Swelling in Neck, Multiple lymph nodes	+	+	+	-	Lymphoproliferative Disorder	THRBCL	Negative	12.87	4.74	5.21	39.13	82.41	27.11	32.9	175.6	15.01	79.74	15.46	0	4.77	0.03
Case 21	59	F	None	Swelling on right side of neck	+	+	+	-	Lymphoproliferative Disorder	THRBCL	Positive	10.9	4.33	16.6	33.3	77.1	25.2	32.7	537	15.1	67.5	23.1	3.2	5.9	0.3
Case 22	22	M	None	Swelling on left side of neck	+	+	+	-	Lymphoproliferative Disorder	PTCL	Negative	14.97	4.49	4.33	40.8	90.9	31.5	34.6	185.1	12.8	50.21	37.49	2.74	8.64	0.92
Case 23	21	F	None	Pain in right side of chest and neck swelling on right side	+	+	+	-	HL	NLPHL	Positive	9.6	3.91	14.3	29.6	75.8	24.6	32.4	364	15.3	76.3	12.5	5.4	5.1	0.7
Case 24	30	F	None	Below left neck swelling	+	+	+	-	HL	NLPHL	Positive	9.65	4.01	6.36	30.69	76.47	24.05	31.45	308.9	19.07	77.2	12.09	0.29	10.28	0.14
Case 25	48	M	None	Swelling in Neck	+	+	+	-	HL	MCCHL	Positive	11.35	4.13	8.45	35.45	85.93	27.5	32.01	231.1	14.6	61.94	21.44	4.2	11.3	1.12
Case 26	54	F	Alleged history of fall on floor while walkig	Swelling in Neck	+	+	+	-	Lymphoma	DLBCL	Negative	8.46	4.07	6.26	27.91	68.58	20.78	30.3	339.6	22.86	68.25	13.93	5.51	11.77	0.54
Case 27	68	F	None	Swelling on right side of face	+	+	+	-	NHL	DLBCL	Negative	8.74	3.94	3.06	33.49	85.33	27.03	31.67	100	14.09	29.52	12.68	46.12	11.04	0.64
Case 28	12	M	None	Neck swelling, emaciation, orthopenia, cough	+	+	+	-	HL	NSCHL	Positive	13.2	4.19	8.51	38.7	92.28	31.47	34.1	274.2	16.32	53.12	28.32	2.53	15.47	0.56
Case 29	60	M	None	Swelling in neck, armpits	+	+	+	-	NHL	DLBCL	Negative	11.7	4.23	6.79	34.1	93.27	33.3	35.1	235.1	18.6	40.6	54.4	4	1	0
Case 30	62	F	None	Loose stool, vomiting, nodular swelling	+	+	+	-	Lymphoma	DLBCL	Negative	10.57	3.42	5.55	31.82	93.13	30.94	33.22	394.9	15.91	52	26	4	18	0

Case 31	48	F	None	Nodular swelling in right thigh	+	+	+	-	HL	MCCHL	Negative	12.4	4.24	2.6	37.2	87.7	29.3	33.4	338	17.4	46	35	6	11	2
Case 32	80	M	Hypothyroidism	Swelling in Neck, difficulty in swallowing	+	+	+	-	High Grade Lymphoma	DLBCL	Positive	12.09	4.14	4.37	37.43	90.4	29.22	32.31	161.4	17.83	50.24	34.22	2.97	11.73	0.84
Case 33	29	F	None	Swelling in neck, armpits	+	+	+	-	Round cell malignancy	ALCL	Positive	12.07	3.9	4.86	36.12	85.7	28.21	32.14	321.7	16.14	51.66	28.88	8.75	10.25	0.46
Case 34	28	M	None	Swollen lymph nodes	+	+	+	-	NHL	ALCL	Positive	12	4.25	6.7	38.1	89.6	28.2	31.5	35.5	17.1	62	26	12	0	0
Case 35	46	F	None	Pain in abdomen, fever on-off	+	+	Hepatosplenomegaly	-	NHL	ALCL	Positive	9.03	3.05	2.37	27.41	89.73	29.56	32.95	85.2	18.32	71.23	22.52	0.19	5.86	0.2
Case 36	60	M	None	Left side neck swelling	+	+	+	-	NHL	PTCL	Negative	9.2	2.05	7.6	21.4	104.3	36.69	35.18	88	19.66	86.6	7.4	0.1	5.5	0.4
Case 37	50	F	None	Left side neck swelling	+	+	+	-	NHL	DLBCL	Negative	11.58	3.89	5.9	33.5	95.1	32.4	34.1	384.1	15.9	55	29.7	6	9	0.3
Case 38	37	F	None	Swollen lymph nodes	+	+	+	-	CHL	LRCHL	Positive	11.8	3.81	6.5	33.7	90.1	31.8	34	389	18.7	52.1	31.5	5.3	9	2.1
Case 39	64	M	None	Diminution of vision progressive in onset	+	+	+	-	Malignant Tumor	DLBCL	Negative	14.2	3.57	11.3	41.7	116.8	39.8	34.1	203	16.3	53.2	27.5	4.6	14.2	0.5
Case 40	35	F	None	Fever, body ache	+	+	+	-	NLPHL	NLPHL	Positive	7.6	2.31	1.8	23.7	102.3	32.8	32.1	43	24.4	55.1	15.9	1	27.2	0.8
Case 41	38	F	None	Left side neck swelling	+	+	+	-	CHL	LRCHL	Negative	11.4	3.53	7.8	36.4	89.3	28.5	31.7	196.2	18.7	47.1	39.9	6.7	6.1	0.2
Case 42	14	M	None	Left side neck swelling	+	+	+	-	HL-MCCHL	MCCHL	Positive	12.39	4.42	6.3	39.07	88.39	28.03	31.72	303.6	16.05	68.76	24.79	0.63	5.5	0.32
Case 43	16	M	None	Swelling in neck, armpits	+	+	+	-	CHL	MCCHL	Positive	11.38	4.5	11.51	35.96	79.92	25.29	31.65	754.7	17.71	79.96	6.44	12.63	0.71	0.26
Case 44	37	M	None	Left side neck swelling	+	+	+	-	HL	LRCHL	Positive	12.31	4.63	1.88	38.25	82.6	26.6	32.19	118.8	17.47	40	57	2	1	0
Case 45	7	M	None	Swollen lymph nodes	+	+	+	-	HL	NLPHL	Positive	10.82	4.057	5.2	32.56	80.26	26.66	33.21	343.3	17.35	32	34	27	7	0
Case 46	73	F	None	Cough with sputum, chest pain	+	+	+	-	HL	MCCHL	Positive	11.56	3.89	4.7	34.02	87.4	29.67	33.96	242.8	17.98	31.64	42.16	13.84	11.18	1.18
Case 47	39	M	None	Left side cervical swelling	+	+	+	-	HL	NLPHL	Positive	13.62	4.7	4.85	43.4	92.4	28.99	31.38	268.5	14.09	70	12	0	18	0
Case 48	25	M	None	Left side swelling of neck	+	+	+	-	HL	MCCHL	Positive	13.77	4.6	7.07	39.33	85.5	29.95	35.02	207.4	12.79	57.55	32.36	1.02	8.64	0.43
Case 49	68	F	None	Seneralise pruritus, swelling in neck	+	+	+	-	HL	NLPHL	Positive	10.5	4.18	5.3	32.5	77.9	25	32.2	130	14.4	82	11	3	4	0
Case 50	23	F	None	Swelling in neck	+	+	+	-	CHL	NSCHL	Positive	11.44	4.42	12.54	35.3	79.8	25.84	32.4	449.7	14.4	50	29	18	3	0
Case 51	17	M	None	Swelling in neck left side	+	+	+	-	HL	MCCHL	Positive	14.09	4.67	3.37	43.13	92.5	30.21	32.67	378.1	21.69	48	29	0	23	0
Case 52	72	M	None	Swelling in neck	+	+	+	-	HL	MCCHL	Positive	11.84	4.33	15.05	37.05	85.6	27.34	31.95	317.9	16.61	76	16	2	4	2
Case 53	7	F	None	Swelling in neck right side	+	+	+	-	HL	MCCHL	Positive	10.88	3.85	12.99	32.15	83.48	28.26	33.85	383.1	13.37	55.18	34.49	1.19	8.81	0.33

Case 54	9	M	None	Asymptomatic, sudden episode of abnormal body movement, uprolling of eyes	+	+	+	-	HL	MCCHL	Positive	10.82	4.29	4.02	33.32	77.68	25.22	32.46	350.6	23.13	30	38	18	14	0
Case 55	40	M	None	Axillary swelling	+	+	+	-	HL	MCCHL	Positive	11.86	4.63	3.11	35.96	77.7	25.62	32.98	230	17.81	11	74	12	3	
Case 56	9	M	None	Swollen lymph nodes	+	+	+	-	HL, Reactive lymphadenitis	NLPHL	Positive	13.4	4.9	7.8	40.8	70.4	22.9	33.27	243.5	17.7	52.3	37.7	3	6.8	0.2
Case 57	24	M	None	Swollen lymph nodes	+	+	+	-	Lymphoproliferative Disorder	LRCHL	Negative	12.8	4.21	3.7	38.7	91.8	30.3	33	394	16.7	29.7	30.2	5.3	33.7	1.1
Case 58	68	M	None	left side swelling of neck	+	+	+	-	HL	LRCHL	Negative	11.6	3.92	8.8	35.4	90.3	29.5	32.7	120	16.7	45.9	35.9	8.7	9.1	0.4
Case 59	55	M	jaundice four month back	fever with chill, wt loss, weakness	+	+	+	+	Chronic Lymphoproliferative disorder	LRCHL	Negative	7.8	2.7	5.3	22	85	27.22	32.7	75	19.1	57	26.1	1	15	0.9
Case 60	32	M	None	Axillary swelling	+	+	+	-	NHL	PTCL	Negative	15.1	4.2	6.8	44.3	105.7	35.9	34	210	15.8	54.2	37.6	2.5	5.5	0.2
Case 61	51	M	Diabetes mellitu, Hypothyroidism	Swelling in neck, armpits	+	+	+	-	Malignant tumor	T-LBL	Negative	12.01	4.19	4.56	35.81	85.56	28.69	33.53	147.4	13.31	68.44	19.38	1.57	10.38	0.23
Case 62	58	F	None	Left side swelling of neck	+	+	+	-	NHL	PTCL	Negative	8.8	2.74	5.6	27.1	98.8	32	32.4	417	20.1	24.5	40.2	8.3	26	1
Case 63	72	M	None	Swelling in neck left side	+	+	+	-	NHL	AITL	Negative	12.3	4.5	7.1	38.53	79.35	29.6	34.1	165	13.4	60.3	23	2.8	13.7	0.2

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