Evaluation of CD47 Expression in B-cell Lymphoma

Alaa Mohammed Abd Al-Rahman* , Khalid Wissam Abdulfattah Khattab* , Nadwa Subhi Alazzo*
*Department of Pathology, College of Medicine, University of Mosul, Mosul, Iraq
Correspondence: alaa.24hmp2@student.uomosul.edu.iq

ABSTRACT

Background: Lymphoma is a malignant lymphoid cell tumors at varying stages of maturity and it is the most common hematological malignancy. Lymphoma is classified mainly into non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Cluster of Differentiation 47(CD47) is cell surface protein, expressed by approximately all cells in the body in addition to different tumor cell types such as lymphoma. It mediates immune homeostasis, cell proliferation, phagocytosis, migration and apoptosis.
Objectives: To evaluate the expression of CD47 in B-cells lymphoma in addition to study the relation of expression of CD47 with some clinicopathological parameters such as site , age and gender.
Methods: A retrospective and prospective case series study of 51 cases of B-cell lymphoma, which were collected from histopathological departments of governmental and private labs over six months extending from September 2024 to February 2025.Assessment of IHC expression of CD47 expression on B-cell lymphoma.
Results: A total of 51 patients, 53% were HL , while 47% were NHL. The age of the patients under 60 years was 45% while at 60 years and above 55%, 64.7% were nodal presentation and 35.3% were extranodal ,51% were males while 49% were females.64.71% were high CD47 expression while 35.29% were low CD47 expression group.
Conclusions: high CD47 expression was associated with female gender and younger age patients, however, long term follows up studies on larger sample is recommended.

Keywords: CD47, B-cell lymphoma, Hodgkin lymphoma, Non Hodgkin lymphoma.

التعبير النسيجي المناعي الكيميائي لـ CD47 في سرطان الغدد اللمفاوية

الاء محمد عبد الرحمن* ، خالد وسام عبد الفتاح خطاب* ، ندوى صبحي العزو*
*فرع علم الامراض ، كلية الطب ، جامعة الموصل ، الموصل ، العراق

الخلاصة

الخلفية: اللمفوما هي أورام خبيثة في الخلايا اللمفاوية في مراحل مختلفة من النضج، وهي أكثر أنواع الأورام الخبيثة شيوعًا في الدم. تُصنف اللمفوما بشكل رئيسي إلى لمفوما غير هودجكينية (NHL) ولمفوما هودجكينية (HL). بروتين مجموعة التمايز ٤٧ (CD47) هو بروتين سطح الخلية، تُعبر عنه جميع خلايا الجسم تقريبًا، بالإضافة إلى أنواع مختلفة من خلايا الورم مثل اللمفوما. يتوسط هذا البروتين التوازن المناعي، وتكاثر الخلايا، والبلعمة، والهجرة، وموت الخلايا المبرمج.

الأهداف: تقييم التعبير عن CD47 في ليمفوما الخلايا البائية، بالإضافة إلى دراسة علاقة التعبير عنه ببعض المعايير السريرية والمرضية، مثل موقع الورم والعمر والجنس.

الطريقة: دراسة حالة استرجاعية ومستقبلية لـ ٥١ حالة من ليمفوما الخلايا البائية، جُمعت من المختبرات الحكومية والخاصة على مدى ستة أشهر، من سبتمبر ٢٠٢٤ إلى فبراير ٢٠٢٥. تقييم التعبير النسيجي المناعي الكيميائي لـ CD47 في ليمفوما الخلايا البائية.

النتائج: شملت الدراسة ٥١ مريضًا، ٥٣% منهم مصابون بلمفوما هودجكين، و٤٧% مصابون بلمفوما غير هودجكين. بلغت نسبة المرضى الذين تقل أعمارهم عن ٦٠ عامًا ٤٥%، بينما بلغت نسبة المرضى الذين تتراوح أعمارهم بين ٦٠ عامًا فأكثر ٥٥%، منهم ٦٤.٧% مصابون بعقد ليمفاوية، و٣٥.٣% مصابون بعقد ليمفاوية خارج ليمفاوية. كان ٥١% من الذكور و٤٩% من الإناث. كان ٦٤.٧١% مصابين بارتفاع مستوى التعبير النسيجي المناعي الكيميائي لـ CD47، بينما كان ٣٥.٢٩% مصابين بانخفاض مستوى التعبير الجيني لـ CD47. الاستنتاجات: ارتبط ارتفاع مستوى التعبير النسيجي المناعي الكيميائي لـ CD47 بالإناث وصغر سن المرضى، ومع ذلك، يُوصى بإجراء دراسات متابعة طويلة الأمد على عينة أكبر.

INTRODUCTION

Lymphoma is a diverse collection of malignant lymphoid cell tumors at varying stages of maturity [1] and it is the most common hematological malignancy [2]. Lymphoma is classified mainly into non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) [3] .Hodgkin lymphoma is a B-cell lymphoid malignancy.The two separate disease entities that make up HL are nodular lymphocyte-predominant HL and classical HL [4].

Non-Hodgkin lymphomas are a diverse category of lymphoproliferative tumors that are significantly less predictable than Hodgkin's lymphomas [5].

In 2024, lymphoma was accounted for 3.3% of cancer-related fatalities in the United States and around 4% of all newly diagnosed cancer cases [6,7].

Cancer cells, including lymphomas and solid tumors, have evolved multiple ways to evade immune detection and destruction, a phenomenon known as immune evasion.Lymphoma cells either evade detection by the immune system [8] or may "defend" themselves to develop resistance against immune eradication [9].

The most crucial element of using immunohistochemical markers (IHC) for lymphoma diagnosis and classification is the type of immunohistochemical marker positivity (nuclear, cytoplasmic, or membrane) and the proportion of cells exhibiting the positivity needed for precise lymphoma classification and differentiation from reactive processes [10].

Immunohistochemistry has important role in confirmation of diagnosis and accurate typing of B cell lymphoma. Many markers such as CD10, MUM1[11],FLT3[12], CD30, CD15, CD20[13] and BCL6[14] are used for this purpose.

Cluster of Differentiation 47(CD47) is a heavily glycosylated 50 Kd cell surface protein.CD47 belongs to the immunoglobulin superfamily, originally named integrin-associated protein (IAP) [15]. It is encoded by gene called CD47 gene located on 3q13.12 region of chromosome in human [16].

CD47 have the ability of interaction with a different ligands and affects many biological functions of target cells by binding to these ligands. It mediates immune homeostasis, cell proliferation, phagocytosis, migration and apoptosis.

The ligands can be extracellular ligands such as signal regulatory protein alpha` (SIRP-a), thrombospondin-1(TSP-1), integrins (a2B1,a4B1,a5B1 and a6B1), CD36, CD95 and signal regulatory protein gamma or intracellular ligands such as Bcl-2/adenovirus E1B 19-KDa interacting protein 3 and Gi proteins [17,18].

CD47 is expressed by approximately all cells in the body [15], widely expressed in different normal human cell types, including B cells, T cells, red blood cells, thymocytes, platelets, monocytes, endothelial, epithelial, neural cells, vascular smooth muscle, fibroblasts and sperm [19]. CD47 is expressed in the membrane of different tumor cell types such as lymphoma, leukemia, gastrointestinal cancer, prostate cancer, lung cancer, and hepatocellular carcinoma [17-19].Lymphoma cells often express CD47 which binds to signal regulatory protein alpha (SIRP-α) on macrophages, sending an inhibitory signal that prevents phagocytosis of tumor cells by innate immune cells [20].

Aim of The Study

To evaluate the expression of CD47 in B-cell lymphoma in addition to study the association of expression of CD47 with some clinicopathological parameters such as type, site, age and gender.

Materials and Method

A retrospective and prospective case series study extending over six month, from September 2024 to February 2025, this study registered all cases diagnosed as B-cell lymphoma at governmental hospitals (Al-Jumhori and Al-Salam teaching hospitals) and those referred from private laboratories in Nineveh province in the north of Iraq. The study included 51 cases of B-cell lymphoma. All histopathological reports were thoroughly reviewed regarding the clinicopathological data, including age, gender and site. We examined the hematoxylin and eosin-stained sections for each case and all HL cases showing positively for CD15 and CD30 while all NHL cases showing positively for CD20.The tumor was diagnosed according to the WHO classification system 2022.

Immunohistochemistry

IHC was done according to the directions provided by the manufacturer of the kit. Each case was studied for CD47 expression, formalin-fixed paraffin –embedded blocks of study samples were obtained and sections of 4 microns thickness were treated with xylene and rehydrated.Heat –based methods for antigen retrieval was used. All sections were put in a pressure cooker containing a solution of 10 mmol/L Tris buffer, 1 mmol/L EDTA, and pH9.0. The immersion lasted for fifteen minutes, then hydrogen peroxide (H2O2) used for inhibiting the inherent peroxidase activity.

The sections were treated with Monoclonal Mouse Anti-CD47/IAP (Integrin Associated Protein) (Medayasis USA)(code MC0027) at dilution range of (1:50) was used , incubated for thirty minutes at room temperature. The primary antibody was detected using the Mouse/Rabbit PolyDetector Plus HRP/DAB solution (code BSB 0265) from the Medaysis. Positive control tissue consisted of colon epithelial cells.

Immunohistochemical markers and clinicopathological factors were evaluated using the statistical package for Social Science version 23 SPSS to assess the correlation between CD47 expression and variable categories were evaluated using the Fisher Exact test and the probability level (P<0.05)considered significant.

Interpretation of CD47 Expression

Evaluation of CD47 expression according to Allred score. The level of staining was classified as 0 (no immunostaining), 1 (weak), 2 (moderate), and 3 (strong); the percentage of chromatosis cells was characterized as 0 (none), 1 (1–10%), 2 (11–50%), 3 (51–80%), and 4 (>80%), Photomicrograph (1).Then multiply these two numbers: 0–2 is classified as (−); 3–4 as (+); 5–8 as (++); and 9–12 as (+++). 0–1+ was classified as low expression, whereas 2–3+ was categorized as high expression [21]. Due to the fact that all HRS cells expressed CD47 with at least weak cytoplasmic and membrane intensity, the scoring was done using a simplified version of the Allred system. Patients with weak or intermediate CD47 expression on HRS cells were categorized as having low CD47 expression on HRS cells. While Cases with high expression of CD47 on HRS cells were identified by a uniform staining pattern and strong intensity of CD47 expression relative to neighboring cells [22].

RESULTS

Among 51 cases included in this study, 27(53%) were diagnosed as HL , whereas 24(47%) diagnosed as NHL. The age of the patients under 60 years was observed in 23 cases (45%) while at 60 years and above, there were 29 cases (55%). In HL, the age of patients ranged from 4-70 years (mean 31.29 y), (median 28 y) and peaked at 20-29 y (8/27), while in NHL, the age of the patients ranged from 23-84 years (mean 62y), (median 66y) and peaked at ≥ 60 years (18/24).

The distribution of the study sample according to the presentation sites, 33 cases (64.7%) had nodal presentation (24 HL and 9 NHL) while extra- nodal presentation was noticed in 18 cases (35.3%) (3 HL and 15 NHL) is showed in figure (1).

Distribution of the study sample according to gender is demonstrated in figure (2) and showed that 26 cases (51%) of the study sample were males while 25 (49%) were females.

The distribution of the study sample according to CD47 expression is demonstrated in figure (3) and showed that 33 cases (64.71%) of the study sample were high CD47 expression while 18 cases (35.29%) were low CD47 expression group.

Comparison of the study parameters in relation to CD47 high and low expression groups is demonstrated in the table below. It revealed that in high CD47 expression group, patients younger than sixty years were more frequent (20 out of 33) (60.6%) but among low CD47 expression group ,it was divided equally between patients younger and older 60 (9 cases for each) ; the difference was statistically not significant (P value=0.3).Females were predominant in high CD47 expression group represented in 19 cases (57.6%) while male were predominant in low CD47 expression group represented in 12 cases (66.7%); the difference was statistically not significant (P value=0.08).Nodal and extranodal presentation showed no statistically significant difference between the study groups although the nodal was more frequent (P value=0.4).NHL were predominant in high CD47 expression group represented in 17 cases (51.5%) while HL were predominant in low CD47 expression group in 11 cases (61.1%); the difference was statistically not significant (P value=0.2).

Table: Comparison of The Study Parameters with CD47 Expression Groups of B- cell Lymphoma.

Characteristics		CD47			p-value
		High	Low	Total	
Age					0.3*
	<60 years	20 (60.6%)	9 (50.0%)	29 (56.9%)	
	≥60 years	13 (39.4%)	9 (50.0%)	22 (43.1%)	
Gender					0.08*
	Male	14 (42.4%)	12 (66.7%)	26 (51.0%)	
	Female	19 (57.6%)	6 (33.3%)	25 (49.0%)	
Presentation site					0.4*
	Extranodal	11 (33.3%)	7 (38.9%)	18 (35.3%)	
	Nodal	22 (66.7%)	11 (61.1%)	33 (64.7%)	
Histological type					0.2*
	HL	16 (48.5%)	11 (61.1%)	27 (52.9%)	
	NHL	17 (51.5%)	7 (38.9%)	24 (47.1%)	

*Fishers Test has been used
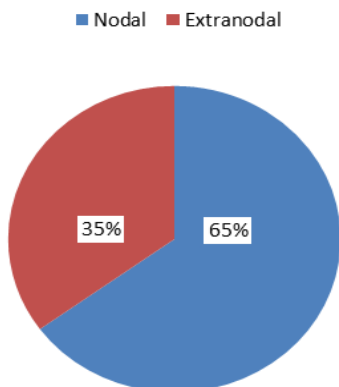
Presenting site

■ Nodal ■ Extranodal

Figure (1) Distribution of the study sample according to presenting site

Gender

■ Females ■ Males
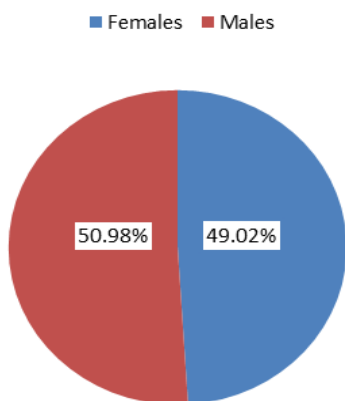

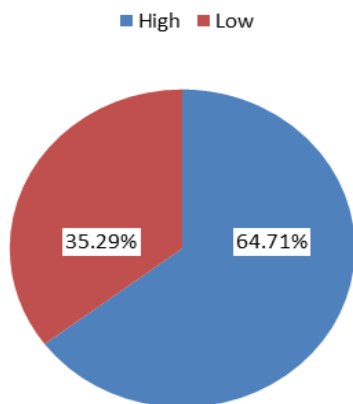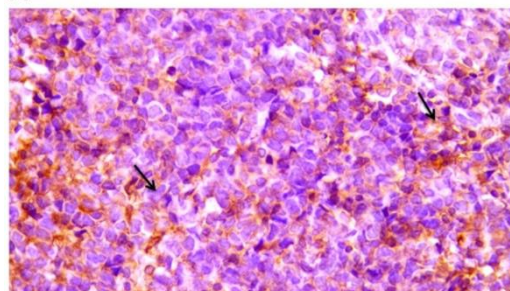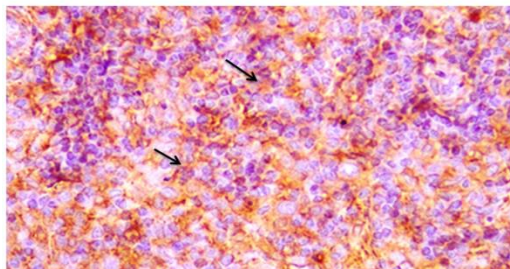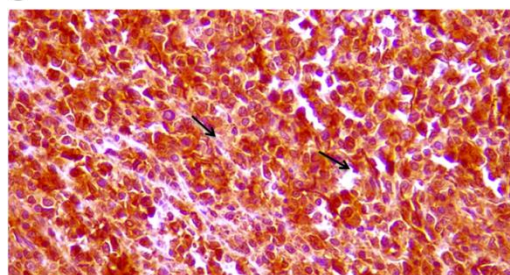Figure (2) Distribution of the study sample according to gender

CD47 expression

■ High ■ Low

Figure (3) Distribution of the study sample according to CD47 expression.

Photomicrograph: IHC expression model of CD47 in B-cell lymphoma according to percentage of staining of cells:(A)Membranous and cytoplasmic brown DAB staining of <50% CD47 expression(black arrow) (×400),(B) Membranous and cytoplasmic brown DAB staining of <80% CD47 expression(black arrow)(×400),(C)Membranous and cytoplasmic brown DAB staining of >80% CD47 expression(black arrow) (×400).

DISCUSSION

B-cell lymphomas are clonal malignancy resulting from the aberrant proliferation of a single B-cell (clone) that result in the development of the tumor [23]. It can be classified according into the presence or absence of RS cells into HL and NHL respectively [24,25].

CD47, a trans-membrane glycoprotein , it is one of the members of immunoglobulin superfamily ,a proximately expressed on the surface of almost all cells of the body in addition to many malignant cells including lymphoma. It provides a "do not eat" signal by binding to the N-terminal region of signal regulatory protein alpha (SIRPα) on immune cells and suppresses phagocytosis of CD47 binding cells [26-28].

High CD47 expression in the current study was prevalent in individuals under sixty (60.6%), agreed with Kiliçarslan A et al. (54.5%)[29] in Turkey and Lopez-Pereira et al. (76.92%)[30] in Austria on classical Hodgkin lymphoma. This contrasts with finding of Cho J et al. in Korea and Kazama et al. in Japan who reported a predominance in individuals aged 60 and older with rates of (56.4%)[31] and (83%)[32] respectively on DLBCL .

This disparity in age predominance may be attributed to demographic variability and difference in the subtypes between our region and Europe and East Asia [33-35].

The current study analysis indicates that high CD47 expression is more prevalent in females than in males (57.6 %), corresponding with the findings of Kazama et al. on DLBCL in Japan (52%) [32]. This finding could be due to CD47 expression is influenced by sex hormones particularly estrogen as there is research indicates that anti-estrogen therapies, such as tamoxifen , can regulate CD47 expression in breast cancer cells [36].

While there were some studies with high CD47 expression in males than in females, such as those by Gholiha et al. on classical Hodgkin lymphoma in Denmark and Sweden (69%)(60%)[22] and Cho J et al. on DLBCL in Korea (18.8%)[31], as male predominance in high CD47 expression lymphoma is likely due to a combination of genetic and molecular differences, variation in the tumor microenvironment and epidemiological factors [37].

Different studies showing high CD47 expression in nodal sites like Gholiha et al.(35%- 38%) on classical Hodgkin lymphoma [22],Starr et al. in his case report also revealed significant CD47 expression in both nodal and intravascular DLBCL cells [38] and these agreed with present study (66.7%).

The difference in the percentage may be explained by variations in scoring criteria, cohort characteristics, tumor biology and subtype. Also our results contrasts with the findings of Chao et al., who identified high CD47 expression of NHL at extra nodal sites (66%)[39]. These discrepancies may be ascribed to the predominance of HL in our region [40,41].

In current study, instances with high CD47 expression show a slightly higher percentage in B cell NHL than in HL (51.5% vs 48.5%). This may be attributed to higher CD47 expression in most subtypes of B cell NHL compared to HL, especially in aggressive B-cell lymphoma like DLBCL[42.] Also in the cases of HL, 59.25% exhibited high CD47 expression. This is higher with what was reported by Gholiha et al. on classical Hodgkin lymphoma in Denmark and Sweden (35%-38%)[22].

This may be due to in the middle eastern population has different HL epidemiology like age distribution, histologic subtypes, genetic background, EBV-associated prevalence compared to Scandinavia [22,43,44] .

On the other hand López-Pereira B et al. in Asturias, reported a uniform high CD47 expression (100%) across all HL study samples, a finding potentially skewed by the limited sample size of only thirteen cases [30]. In the current cases of B cell NHL, CD47 expression was high in (70.83%) of instances. In light of the lack of supplementary studies particularly addressing NHL, cited research concentrating on the predominant subtype of our NHL cases, namely DLBCL like by Kazama et al. in Japan reported 59% [32], Shen YG et al.in China, reported 65.5% [45], and Chao et al.in US, reported 16.4% for DLBCL [39]. In DLBCL the cancer cells increase the expression of CD47 in order to help them to evade the immune system, especially from macrophages in addition to changes in the genes of lymphoma like 18q21 gain in addition to high MYC protein which make the cancer grow faster [46,47].

According to the results of this study ,high CD47 expression in B-cell lymphoma may support the rationale for incorporating CD47 blockade in B-cell lymphoma treatment as overexpression of CD47 has been associated with poor prognosis in B-cell lymphomas [48]. Different approach target CD47/SIRP-α axis have been appeared and changed from preclinical studies to early clinical trials such as CD47 targeting agents ,like Magrolimab (Hu5F9-G4), a humanized monoclonal IgG4 antibody, it inhibits CD47 signaling, which lead to increases macrophage phagocytosis ,it also activates Antibody-dependent cell-mediated cytotoxicity (ADCC)[48]. The combination of Magrolimab with rituximab (anti CD20, cytotoxic drug) make magrolimab more effective than alone especially in patients with diffuse large B-cell lymphoma and follicular lymphoma [49-51].

Limitation of The Study

The current study has some limitations, including a small sample size, lack of case diversity and absence of patient follow-up.

CONCLUSION

CD47 is an important immunohistochemical marker having therapeutic implications. High expression associated with female gender and younger age patients, however, long term follows up studies on larger sample is recommended to elicit the prognostic role of CD47 expression in B-cell lymphoma cases in Iraq.

Conflict of Interest

No conflict of interest.

Ethical Approval

This study was reviewed and approved by the Medical Research Ethnic (MREC), College of Medicine, University of Mosul (Iraq) . This study approved by the Research Committee of Nineveh Health Directorate with a research protocol (2024155) by Decision number (259) in 4/9/2024.

REFERENCES

1. Rafea H, Al-Tae AK, Jawhar N. Diagnostic Yield of PAX5 in Lymphoma. Ann Coll Med Mosul. 2021;42(2):109–18. doi: 10.33899/mmed.2020.128737.1058.

2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7–33.doi: 10.3322/caac.21654.

3. Ennishi D, Hsi ED, Steidl C, Scott DW. Toward a new molecular taxonomy of diffuse large B-cell lymphoma. Cancer Discov. 2020;10(9):1267–81. doi: 10.1158/2159-8290.cd-20-0174.

4. Ansell SM. Hodgkin lymphoma: 2023 update on diagnosis, risk-stratification, and management. Am.J.Hematol. 2022 Nov;97(11):1478-88. doi: 10.1002/ajh.26717.

5. Kshatri JS, Satpathy P, Sharma S, Bhoi T, Mishra SP, Sahoo SS. Health research in the state of Odisha, India: a decadal bibliometric analysis (2011-2020). J Fam Med Prim Care. 2022 Jul 1;11(7):3771-6. doi: 10.4103/jfmpc.jfmpc_2192_21.

6. Kundu R, Kal N, Singh A, Jagadeesh D. Global Incidence, Mortality and Risk Factors of Hodgkins and Non-Hodgkins Lymphoma 1990-2021: A Global Health Data Study. Blood. 2024 Nov 5;144:6360. doi:10.1182/blood-2024-212117.

7. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024 Jan;74(1):12-49. doi: 10.3322/caac.21820.

8. de Charette M, Houot R. Hide or defend, the two strategies of lymphoma immune evasion: potential implications for immunotherapy. haematologica. 2018 Jul 13;103(8):1256 doi:10.3324/haematol.2017.186650.

9. Ansell SM, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372:311-319. doi:10.1056/NEJMoa1411087.

10. Borgohain M, Krishnatreya K, Weingken CK, Das JK. Diagnostic Utility of Immunohistochemistry in Lymphoma Section. Int J Contemporary Med Res. 2017;4(12):6-9. ISSN (Online):2393-915×;(Print):2454-7379.

11. Zuhair Z, Khattab KW. The Utility of CD10 and MUM1 Immunohistochemical Stains in Subtyping Diffuse Large B Cell Lymphoma. J Nat Sci Biol Med. 2024 Jan;15(1):51-7. doi:10.4103/jnsbm.JNSBM_15_1_6.

12. Fahad LA, Al-Omar ZM, AL-Kheroo KN. Characterization of the FLT3 Mutation in Newly Diagnosed Patients with Acute Myeloid Leukemia. Al-Anbar Med J. 2024 Jun 1;20(1). doi:10.33091/amj.2024.144737.1447.

13. Fadhil MS, Al-Nueimy WM, Lazim AF. Hodgkin's lymphoma. An immunohistochemical profile in northern Iraq. Saudi Med J. 2014 May;35(5):448-53. PMID: 24825804.

14. Jameel ZZ, Khattab KW. BCL6 Immunohistochemical Expression In Diffuse Large B Cell Lymphoma. Ann Coll Med Mosul. 2024 Jun 1;46(1):43-0. doi:10.33899/mmed.2024.145600.1245.

15. Eladl E, Tremblay-LeMay R, Rastgoo N, Musani R, Chen W, Liu A, et al. Role of CD47 in hematological malignancies. J Hematol Oncol. 2020 Dec;13:1-4. doi:10.1186/s13045-020-00930-1.

16. Huang CY, Ye ZH, Huang MY, Lu JJ. Regulation of CD47 expression in cancer cells. Transl Oncol. 2020 Dec 1;13(12):100862. doi:10.1016/j.tranon.2020.100862.

17. Yang H, Xun Y, You H. The landscape overview of CD47-based immunotherapy for hematological malignancies. Biomark Res. 2023 Feb 1;11(1):15. doi:10.1186/s40364-023-00456-x.

18. Huang J, Liu F, Li C, Liang X, Li C, Liu Y, et al. Role of CD47 in tumor immunity: a potential target for combination therapy. Sci Rep. 2022 Jun 13;12(1):9803. doi:10.1038/s41598-022-13764-3.

19. Zhao P, Xie L, Yu L, Wang P. Targeting CD47-SIRPα axis for Hodgkin and non-Hodgkin lymphoma immunotherapy. Genes Dis. 2024 Jan. doi:10.1016/j.gendis.2022.12.008.

20. Qu T, Li B, Wang Y. Targeting CD47/SIRPα as a therapeutic strategy, where we are and where we are headed. Biomark Res. 2022;10:20. doi:10.1186/s40364-022-00373-5.

21. Yang K, Xu J, Liu Q, Li J, Xi Y. Expression and significance of CD47, PD1 and PDL1 in T-cell acute lymphoblastic lymphoma/leukemia. Pathol Res Pract. 2019 Feb 1;215(2):265-71. doi:10.1016/j.prp.2018.11.007.

22. Gholiha AR, Hollander P, Löf L, Glimelius I, Hedstrom G, Molin D, et al. Checkpoint CD47 expression in classical Hodgkin lymphoma. Br J Haematol. 2022 Jun;197(5):580-9. doi:10.1111/bjh.18137.

23. Alizadeh AA, Aranda V, Bardelli A, Blanpain C, Bock C, Borowski C, et al. Toward understanding and exploiting tumor heterogeneity. Nat. Med. 2015 Aug;21(8):846-53. doi:org/10.1038/nm.3915.

24. Aslani A, Morsali S, Mousavi SE, Choupani S, Yekta Z, Nejadghaderi SA. Adult Hodgkin lymphoma incidence trends in the United States from 2000 to 2020. Sci. Rep. 2024 Sep 3;14(1):20500.
doi:10.1038/s41598-024-69975-3.

25. Kumar V, Abbas A K & Aster J C. Robbins Basic Pathology . 2018 (10th ed., vol.12, p 463). Elsevier .

26. Huang Y, Ma Y, Gao P, Yao Z. Targeting CD47: the achievements and concerns of current studies on cancer immunotherapy. J Thorac Dis. 2017 Feb;9(2):E168.
doi:10.21037/jtd.2017.02.30.

27. Velliquette RW, Aeschlimann J, Kirkegaard J, Shakarian G, Lomas-Francis C, Westhoff CM. Monoclonal anti-CD47 interference in red cell and platelet testing. Transfusion. 2019 Feb;59(2):730-7. doi:10.1111/trf.15033.

28. Wiewiora M, Piecuch J, Sedek L, Mazur B, Sosada K. The effects of obesity on CD47 expression in erythrocytes. Cytometry B Clin Cytom. 2017 Nov;92(6):485-91. doi:10.1002/cyto.b.21232.

29. Kiliçarslan A, Kurt Çevik G, Doğan M, AKSOY ALTINBOĞA AY, Ceran F, BAKANAY ÖZTÜRK ŞM, et al. Does CD47 expression have prognostic significance in classical Hodgkin lymphoma?. Turk J Med Sci. 2025;55(1):203-8. doi:10.55730/1300-0144.5958.

30. López-Pereira B, Fernández-Velasco AA, Fernández-Vega I, Corte-Torres D, Quirós C, Villegas JA, et al. Expression of CD47 antigen in Reed–Sternberg cells as a new potential biomarker for classical Hodgkin lymphoma. Clin Transl Oncol. 2020 May;22:782-5.doi:10.1007/s12094-019-02171-2.

31. Cho J, Yoon SE, Kim SJ, Ko YH, Kim WS. CD47 overexpression is common in intestinal non-GCB type diffuse large B-cell lymphoma and associated with 18q21 gain. Blood Adv. 2022 Dec 27;6(24):6120-30.
doi:10.1182/bloodadvances.2021006305.

32. Kazama R, Miyoshi H, Takeuchi M, Miyawaki K, Nakashima K, Yoshida N, et al. Combination of CD47 and signal-regulatory protein-α constituting the "don't eat me signal" is a prognostic factor in diffuse large B-cell lymphoma. Cancer Sci. 2020 Jul;111(7):2608-19. doi:10.1111/cas.14437.

33. Sun H, Xue L, Guo Y, Du J, Nan K, Li M. Global, regional and national burden of non-Hodgkin lymphoma from 1990 to 2017: estimates from global burden of disease study in 2017. Ann Med. 2022 Dec 31;54(1):633-45. doi:10.1080/07853890.2022.2039957.

34. Muhealdeen DN, Shwan A, Yaqo RT, Hassan HA, Muhammed BO, Ali RM, et al. Epstein-Barr virus and Burkitt's lymphoma. Associations in Iraqi Kurdistan and twenty-two countries assessed in the International Incidence of Childhood Cancer. Infect Agents Cancer. 2022 Jul 27;17(1):39. doi:10.1186/s13027-022-00452-0.

35. Testi AM, Al-Jadiry MF, Moleti ML, Uccini S, Al-Darraij AF, Al-Saeed RM, et al. Hodgkin Lymphoma in children: a 16-year experience at the Children's Welfare Teaching Hospital of Baghdad, Iraq. Mediterr J Hematol Infect Dis. 2024 Jul 1;16(1):e2024053. doi:10.4084/mjhid.2024.053.

36. Cook KL, Soto-Pantoja DR. "UPRegulation" of CD47 by the endoplasmic reticulum stress pathway controls anti-tumor immune responses. Biomark Res. 2017 Dec;5:1-6. doi:10.1186/s40364-017-0105-8.

37. Huang D, Berglund M, Damdimopoulos A, Antonson P, Lindskog C, Enblad G, Amini RM, Okret S. Sex-and Female Age-Dependent Differences in Gene Expression in Diffuse Large B-Cell Lymphoma—Possible Estrogen Effects. Cancers. 2023 Feb 17;15(4):1298. doi:10.3390/cancers15041298.

38. Starr JS, Jiang L, Li Z, Qiu Y, Menke DM, Tun HW. CD47 and osteopontin expression in diffuse large B-cell lymphoma with nodal and intravascular involvement. Clin Lymphoma Myeloma Leuk. 2013 Oct 1;13(5):597-601. doi:10.1016/j.clml.2013.05.001.

39. Chao MP, Tang C, Pachynski RK, Chin R, Majeti R, Weissman IL. Extranodal dissemination of non-Hodgkin lymphoma requires CD47 and is inhibited by anti-CD47 antibody therapy. Blood. 2011 Nov 3;118(18):4890-901.doi:10.1182/blood-2011-02-338020.

40. Monabati A, Safaei A, Noori S, Mokhtari M, Vahedi A. Subtype distribution of lymphomas in South of Iran, analysis of 1085 cases based on World Health Organization classification. Ann Hematol. 2016;95(4):613-618. doi:10.1007/s00277-016-2590-5.

41. Aladily TN, Khreisat W, Ashukhaibi O, Alkhatib SM, Annab H, Tarawneh MS, et al. The epidemiology of lymphoma in Jordan: A nationwide population study of 4189 cases according to World Health Organization classification system .Hematol Oncol Stem Cell Ther. 2021 Oct 1;14(4):336-42.doi:10.1016/j.hemonc.2020.10.002.

42. Chao MP, Alizadeh AA, Tang C, Myklebust JH, Varghese B, Gill S, et al. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. Cell. 2010 Sep 3;142(5):699-713. doi:10.1016/j.cell.2010.07.044.

43. Ahmed HA, Raslan WF, Deifalla AH, Fathallah MD. CD163 is a predictive biomarker for prognosis of classical Hodgkin's lymphoma in Saudi patients. Mol Clin Oncol. 2019 Jul;11(1):67-76. doi:10.3892/mco.2019.1850.

44. Salati M, Cesaretti M, Macchia M, El Mistiri M, Federico M. Epidemiological overview of Hodgkin lymphoma across the mediterranean basin. Mediterr J Hematol Infect Dis. 2014 Jul 1;6(1):e2014048. doi:10.4084/mjhid.2014.048.

45. Shen YG, Ji MM, Yi HM, Shen R, Fu D, Cheng S, et al.CD47 overexpression is related to tumour-associated macrophage infiltration and diffuse large B-cell lymphoma progression. Clin Transl Med. 2024 Jan 9;14(1):e1532.doi:10.1002/ctm2.1532.

46. Bouwstra R, He Y, de Boer J, Kooistra H, Cendrowicz E, Fehrmann RS, et al. CD47 expression defines efficacy of rituximab with CHOP in non–germinal center B-cell (non-GCB) diffuse large B-cell lymphoma patients (DLBCL), but not in GCB DLBCL. Cancer Immunol Res. 2019 Oct 1;7(10):1663-71.doi:10.1158/2326-6066.cir-18-0781.

47. Lee WY, Perry AM, Azcutia V, Herrera AF, Skrabek P, Jackson R, et al. Upregulation of CD47 Expression in De Novo Diffuse Large B-Cell Lymphoma Is More Frequent in Activated B-Cell Type. Blood. 2021 Nov 23;138(Supplement 1):3507-.doi:10.32388/9m8mla.

48. Gholamin S, Mitra SS, Feroze AH, Liu J, Kahn SA, Zhang M, et al. Disrupting the CD47-SIRPα anti-phagocytic axis by a humanized anti-CD47 antibody is an efficacious treatment for malignant pediatric brain tumors. Sci Transl Med. 2017 Mar 15;9(381):eaaf2968. doi:10.1126/scitranslmed.aaf2968.

49. Advani R, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, et al. CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. N Engl J Med. 2018 Nov 1;379(18):1711-21. doi:10.1056/NEJMoa1807315.

50. Yu J, Li S, Chen D, Liu D, Guo H, Yang C, et al. SIRPα-Fc fusion protein IMM01 exhibits dual anti-tumor activities by targeting CD47/SIRPα signal pathway via blocking the "don't eat me" signal and activating the "eat me" signal. J Hematol Oncol. 2022 Nov 16;15(1):167. doi: 10.1186/s13045-022-01385-2.

51. Sikic BI, Lakhani N, Patnaik A, Shah SA, Chandana SR, Rasco D, et al. First-in-human, first-in-class phase I trial of the anti-CD47 antibody Hu5F9-G4 in patients with advanced cancers. J Clin Oncol. 2019 Apr 20;37(12):946-53.doi: 10.1200/JCO.18.02018.