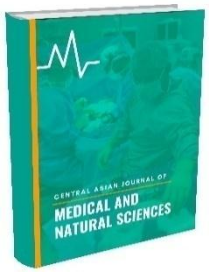
CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES



Volume: 05 Issue: 01 | Jan-Feb 2024 ISSN: 2660-4159

http://cajmns.centralasianstudies.org

EVALUATION THE ROLE OF HEPCIDIN IN LYMPHOMA PATIENTS

1. **Lelas Farhan Bdaiwi**
2. **Alauldeen Alqasim**
3. **Yusur Farhan Bdaiwi**

Received 20th Nov 2023,
Accepted 28th Dec 2023,
Online 29th Jan 2024

[1] University of Mosul, College of Education for Girls, Department of Chemistry, Mosul, Iraq

[2] HMDN, Nottingham University Hospitals, UK

[3] Specialist doctor (Haematopathologist) M. B. Ch. B,FICM. Path At Ibn-Sina teaching hospital Mosul health directorate, Mosul, Iraq

Abstract: Background: Lymphoma are group of diseases caused by malignant Lymphocyte that accumulate in lymph nodes and cause the characteristic clinical features of lymphadenopathy. Anaemia is a common feature in lymphoproliferative disease. Hepcidin: is a liver produced acute phase peptide whose overproduction leads to iron limited erythropoiesis. **Aim of the study:** To assess the level of hepcidin in newly diagnosed lymphoma patients. And correlate it with Hb, stage of disease, bulky disease, and B-symptoms. Patients and methods: Forty patients with newly diagnosed lymphoma were consequently selected from the haematology outpatient clinic at the Medical City24 of them were male and 16 were female. The level of hepcidin was investigated by ELISA technique. **Results:** The mean age for Lymphoma participants in this research was 43. 6±20. 2 years with range of (14-79) years. M:F ratio was 1. 5:129 patients were anaemic with Hb less than 12g /dL, 21patients had stage IV disease (52. 5%), 7 patients had stage III disease (17. 5%),12 patients had stage II disease (30%). Hepcidin level was significantly increased in lymphoma Patients than control group. There was significant inverse relationship between hepcidin with Hb level. There was significant positive relationship between hepcidin level with the presence of B-symptoms and stage of the disease. **Conclusion:** Hepcidin level was significantly increased in lymphoma patients compare to healthy control. It was significantly higher in lymphoma patient with anaemia than no anaemic patients. The adverse impact of elevated hepcidin is consistent with demonstration of higher level of hepcidin in patients with B symptoms and advanced stages.

Key words: hepcidin, lymphoma, Anaemia.

Introduction:

Lymphomas are a diverse group of malignancies of B-cells, T-cells and uncommon natural killer cells that usually originate in the lymph nodes, but may affect any organ of the body [1]. There are two basic categories of lymphomas. one kind is Hodgkin lymphoma (named after Dr. Thomas Hodgkin who first recognized it) which is marked by the presence of a type of cell called the Reed-stern berg cell. The other category is non-Hodgkin lymphomas which include a large, diverse group of cancer[2]. Lymphoma patients typically presents with lymphadenopathy that has been detected either incidentally by the patient or by imaging procedures performed for assessment of other condition, occasionally it may be detected when investigation of non-specific symptoms, such as fever, fatigue, or unexplained pain prompt assessment that in turn reveal mass lesion[3]. Whenever a clinical lymphoma diagnosis is suspected, the surgeon ought to take an open biopsy of the most affected lymph node. When possible, the lymph node should be removed intact because assessing the architecture is crucial for the diagnosis and categorization of lymphomas. The pathologist will fix the tissue for regular histology and for particular research after receiving the lymph node in the pathology laboratory as soon as possible in its fresh form. [4] Single-cell suspensions made from tissue samples can be used for automated flow cytometry to diagnose lymphoma. [5]. Additionally, it establishes the pattern of surface markers' expression that aids in subclassifying lymphomas. [6]. A wide variety of antibodies that can be used on formalin-fixed tissue now are available, allowing accurate diagnosis and subclassification of lymphoma in most cases by immunohistochemistry[7]. Molecular genetic techniques to determine B-or T-cell monoclonality or lymphoma-specific chromosomal translocations include polymerase chain reaction (PCR), Southern blot, fluorescence in situ hybridization (FISH), and cytogenetic analysis [6]

Staging of Lymphoma according to Ann-Arbor staging system. [8]

Anemia in lymphoma: Anemia is a common feature in lymphoproliferative disease even before patients have received cytotoxic therapy and even when there is no bone marrow involvement, the pathogenesis of this anemia, although unclear seems to result from multifactorial factors which include bone marrow involvement abnormal iron reutilization, inappropriately low serum erythropoietin levels for the degree of anemia and a decrease of bone marrow response to erythropoietin, also inflammatory mediator plays important roles in anemia in lymphoma that have been shown to inhibit erythropoiesis such as Interlukin-1 and Interlukin-6, hemolytic anemia secondary to lymphoproliferative disease [9].

Anemia in lymphoma can be roughly categorized into two groups.:

CIA (cancer induced anemia) anemia which is caused by the cancer and the causes seem to be multifactorial for example restrained erythropoiesis by B. M infiltration of tumor, IDA secondary to blood loss, suppression of iron utilization effected by cytokine liberated from tumor cell and bad nutrition for lymphoma patients.

2-TIA (therapy caused anemia) which induced by treatment with anticancer, usually chemotherapy that suppress hematopoiesis of BM [10].

The interaction between the neoplastic cells and the reactive cells of the micro environment, result in high level for cytokines, like IL-6, IL-10. [11]. Through a transcriptional mechanism that is dependent on the signal transducer and activator of transcription 3 (STAT3), IL-6 is a powerful inducer of hepcidin expression. [12] In about 40% of people with lymphoma (HL), anemia is a presenting symptom. It commonly occurs in advanced phases and is more frequently seen in conjunction with B-symptoms such fever, nocturnal sweats, and weight loss. [13]. Hb level showed significant decrease with increasing stage of the disease [14].

Hepcidin: is a liver produced acute phase peptide whose overproduction leads to iron-limited erythropoiesis[15]. Inflammatory cytokines (IL-6) increase the expression of hepcidin leading to decrease iron absorption from the intestine, and block the release of iron from the macrophage of reticuloendothelial system and the liver [16]. A pathogenic cascade linking IL-6, hepcidin, hypoferremia, and anemia inflammation has been postulated as the mechanism by which anemia inflammation develops. [17] Under physiological conditions, hepatic hepcidin expression is elegantly regulated by a cohort of proteins that are expressed in hepatocytes, including the hereditary hemochromatosis (HH) protein called HFE, transferrin receptor 2 (TfR2), hemojuvelin (HJV), bone morphogenetic protein 6 (BMP6), matriptase-2 and transferrin. Hepcidin expression can also be regulated by erythroid factors, hypoxia, and inflammation, regardless of body iron levels [18]. At transcriptional level, hepcidin expression has been regulated by 3 major molecular pathways are: Janus kinase /signal transducer and activator of transcription (JAK/STAT), bone morphogenetic protein/ mothers against decapentaplegic (BMP/SMAD), and hereditary hemochromatosis protein /transferrin receptor 2 (HFE/TfR2) [19].

Materials and methods:

Subject

This case-control investigation was done on 40 newly diagnosed lymphoma patients including (18 with HL, 22 NHL) and 33 healthy control from July 2016 to December 2016. The study was approved by the Iraqi council for medical specialization.

The study population consisted of 40 patients. The patients were attending the hematology out patient clinic at Baghdad teaching hospital,Teaching laboratory of the medical city and the flowcytometry unit at nursing home hospital in Baghdad. A verbal consent was obtained from each patients for accepting to taking P. B sample.

The diagnosis was made by LN biopsy examination with I. H. C by expert histopathologist with blood film, BMA and BMB examination by expert hematopathologist at Teaching laboratory and immune phenotyping study using a four-colour flow cytometry at Nursing home hospital. CBC, blood film, retic count, estimation of hepcidin by ELISA was done for each patients.

Exclusion criteria:

1. patients with lymphoma who received chemotherapy excluded from this study.
2. lymphoma patients with hemolytic anemia (confirmed by high retic count) excluded from this study.

The Control:

A 33 healthy control age and sex matched with the patients group, the control were not diabetic nor hypertensive, not anemic (confirmed by C. B. C), don't have acute illness or inflammation process (confirmed by C. R. P). C. B. C, blood film, C. R. P, Hepcidin level was done for each control subject.

Method: blood sample:

a total of 2. 5 ml of venous blood was collected by clear venipuncture into an EDTA tube, C. B. C, was done by automated Abbott ruby hemolyzer at teaching lab of medical city. blood film and retic count were done for the patients, then the remaining of samples were centrifuged for 10 minutes at 2000 g. plasma sample was stored at -80c at central blood bank of medical city. The plasma was used for estimation of hepcidin level, by ELISA using stander enzymatic reader.

Results:

Seventy three participants were recruited in this study including 40 lymphoma patients(HL & NHL) and 33 healthy control.

Age distribution (years)

There was no significant difference between lymphoma patients and healthy control regarding the age (p. value = 0. 981) as shown

in the table (1), this confirm that the control group were age matched with the patients

Table 1: Age distribution in lymphoma patient compare to control group

		Lymphoma		Healthy control		P value
		No	%	No	%	
	Mean±SD (Range)	43. 6±20. 2 (14-79)		40. 4±19. 1 (14-69)		
Age (years)	<45	21	52. 5	18	54. 5	0. 981
	=>45	19	47. 5	15	45. 5	
*Significant difference between proportions using Pearson Chi-square test at 0. 05 level.						

2- Gender difference

There was no significant difference between lymphoma patients and healthy control groups regarding the gender (the p value was 0. 215) as shown in the table (2), this confirm that the control group were sex matched with the patients.

Table 2: Gender difference between lymphoma patient and control

		Lymphoma		Healthy control		P value
		No	%	No	%	
Gender	Male	24	60. 0	15	45. 5	0. 215
	Female	16	40. 0	18	54. 5	
*Significant difference between proportions using Pearson Chi-square test at 0. 05 level.						

Table (3): Clinical characteristic of lymphoma patients

		Lymphoma	
		No	%
Hepatomegaly	Positive	5	12. 5
	Negative	35	87. 5
Splenomegaly	Positive	22	55. 0
	Negative	18	45. 0
Diagnosis	HL	18	45. 0
	NHL	22	55. 0
B-symptom	Positive	26	65. 0
	Negative	14	35. 0
Bulky disease	Positive	5	12. 5
	Negative	35	87. 5
B. M. involvement	Positive	11	27. 5
	Negative	29	72. 5
Stage	Stage I	-	-
	Stage II	12	30. 0
	Stage III	7	17. 5
	Stage IV	21	52. 5
HL stage	I	0	0
	II	10	55. 5
	III	3	16. 6
	IV	5	27. 7

NHL stage	I	0	0
	II	2	9. 1
	III	4	18. 2
	IV	16	72. 7

3- Anemia in lymphoma patients:

Hemoglobin mean level was 10. 02 ± 1. 93g\dl, the range was 7-13g\dl.

29 patients from 40 lymphoma patients were anemic with hemoglobin (g/dl) level below 12 (g/dl) and 11 patients were not anemic with hemoglobin ≥ 12 (g/dl) as shown in table (3-4).

Table (4): Hb level in HL and NHL patients

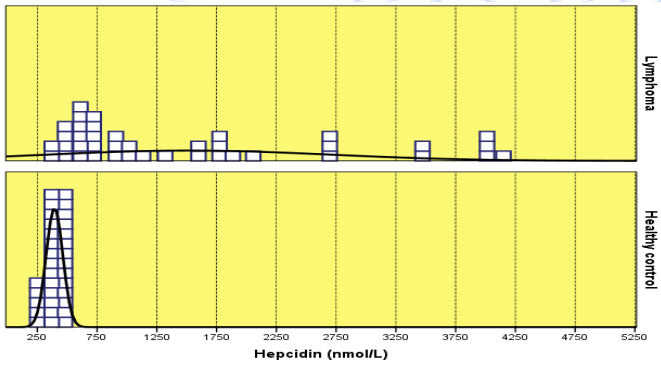
		HL		NHL	
		No	%	No	%
Haemoglobin (g/dL)	<12	9	50. 0	20	90. 9
	=>12	9	50. 0	2	9. 1

4 -Hepcidin level (nmol/l)

Hepcidin mean level was much higher in lymphoma patient compare with healthy control (p. value was 0. 0001) as shown in table (5).

Table (5) Hepcidin level in HL and NHL

Hepcidin (nmol/L)	HL	NHL
No	18	22
Mean±SD	879. 49±587. 81	2043. 24±1299. 56
Range	413. 372-2670. 202	555. 334-4150. 419



P=0. 0001

Figure (1) Hepcidin level in lymphoma patients compare to control group

5- Relationship between hepcidin and Hb:

hepcidin level were significantly higher in patients with hemoglobin < 12 than patients group with hemoglobin ≥ 12 g/dl,as shown in figure (2).

(r= -0. 849)

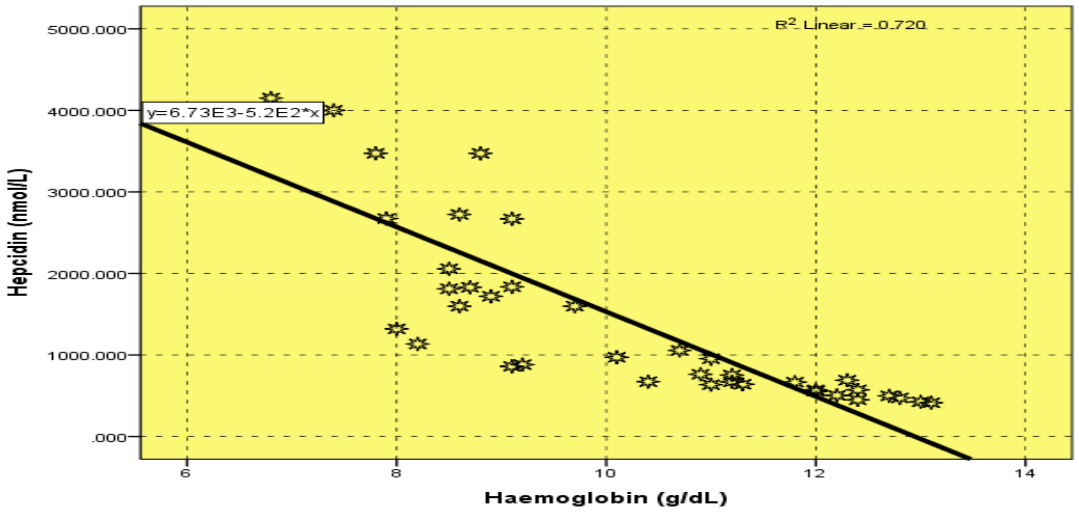


Figure (2) relationship between Hepcidin and Hb

6 - Relationship of hepcidin with some variable:

- **With gender:**

there is no significant deference in hepcidin level between male and female patients

- **B-symptoms:**

There is +ve relationship between hepcidin and B-symptomes

- **Bulky disease:**

There is no significant correlation between hepcidin level and Bulky disease

- **Stage of the disease:**

hepcidin level show strong +ve relationship with the stage of the disease As shown in table (6), figure (3).

Table (6): relationship between Hepcidin with other variable in HL and NHL

Hepcidin (nmol/L)		HL (n=18)		NHL (n=22)	
		No	Mean±SD	No	Mean±SD
Age (years)	<45	14	911. 14±613. 48	7	1880. 32±1391. 86
	=>45	4	768. 73±553. 21	15	2119. 28±1297. 52
	P value		0. 682		0. 698
Gender	Male	9	1104. 99±759. 09	15	2171. 41±1323. 63
	Female	9	653. 99±208. 79	7	1768. 59±1301. 52
	P value		0. 100		0. 072
B-symptom	Positive	10	1114. 99±708. 14	16	2271. 39±1247. 92
	Negative	8	585. 12±126. 99	6	1434. 85±1345. 57
	P value		0. 0054*		0. 018*
Bulky disease	Positive	2	1427. 32±413. 34	3	3152. 83±1190. 07
	Negative	16	811. 01±578. 95	19	1868. 05±1255. 14
	P value		0. 169		0. 113
Stage	Stage I	-	-	-	-
	Stage II	10	531. 53±99. 00	2	563. 96±12. 20
	Stage III	3	778. 68±96. 53	4	731. 21±99. 60
	Stage IV	5	1635. 91±645. 15	16	2556. 16±1153. 68

	P value		0. 0001*		0. 001*
Haemoglobin (g/dL)	<12	9	1237. 42±660. 17	20	2191. 17±1270. 14
	=>12	9	521. 56±100. 77	2	563. 96±12. 20
	P value		0. 005*		0. 009*
*Significant difference between two independent means using Students-t-test or significant difference among more than two independent means using ANOVA test at 0. 05 level.					

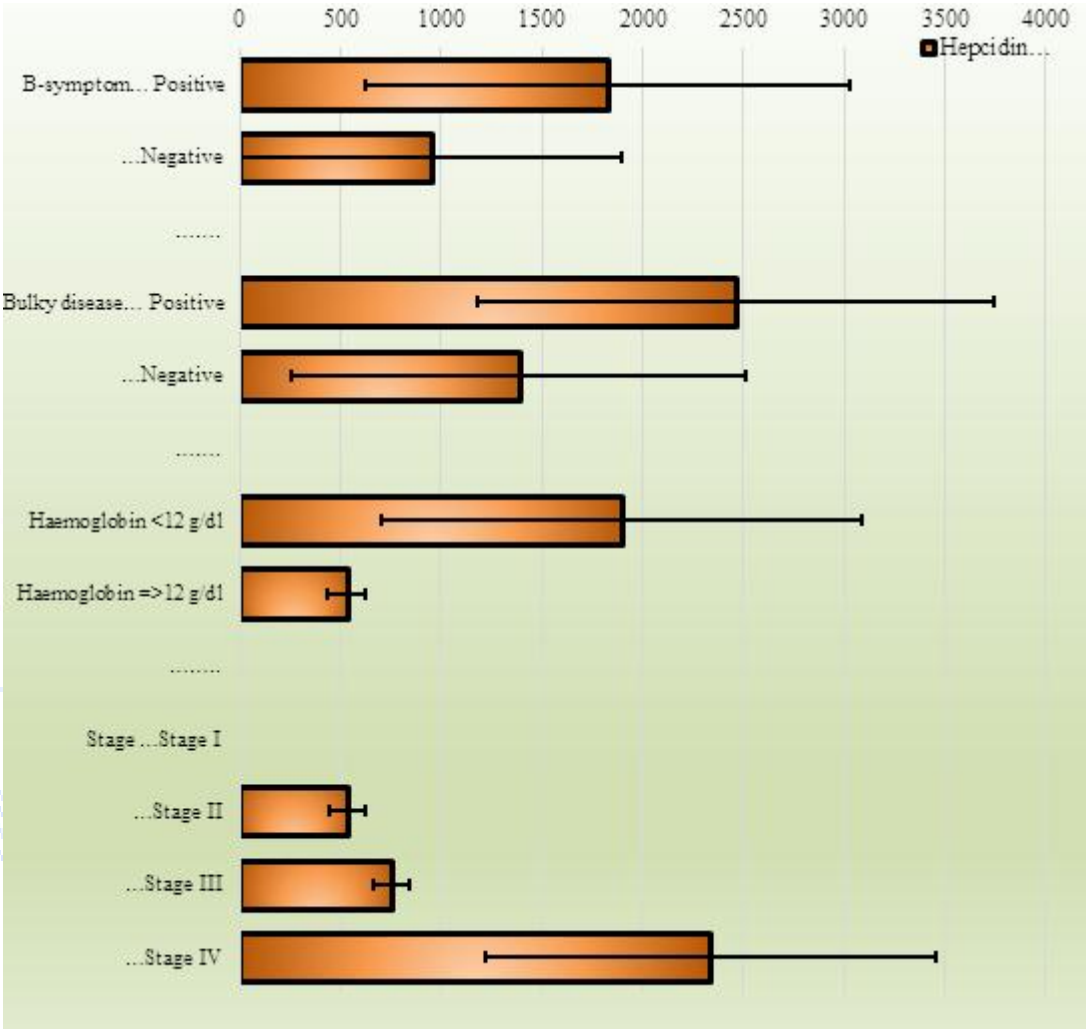


Figure (3): Relationship of hepcidin with some variable

Discussion

In this study the aim was to evaluate the change in hepcidin level, its role in the development of anemia and its correlation with Hb, stage of disease, bulky disease, B-symptoms, age, and gender.

In the current study the mean age for HL was (30. 4 ± 17. 8) year, and the range was(14-69) year, this finding was comparable to a study done by Fadhil MS. et al [20],Iraqi cancer registry 2009 [21],Yaqo RT. et al [22],however the higher age of the lower limit seen in our study may be explained by the fact that our center deals with adult patients.

In this study the mean age for NHL patient was 54. 4±5. 1 year and the range was 26-79 year,this finding was comparable with a study done by Alwan AF. et al [23], Kamil TS. et al [24]

In this study male to female ratio for HL patient was 1:1 this finding was comparable with a study done by Biggar RJ et al [25], but

does not agree with Yaqo RT. et al [22]Fadhil MS. et al [20], who found a male predominance with male to female ratio was 1. 6:1, this may be explained by smaller size sample and ethnicity. This study show that male to female ratio for NHL patient was 2. 1:1, this finding agree with the finding of Iraqi cancer registration [21] Yaqo RT. et al [22] Alwan AF. et al [23]

The current study show that 18 patients out from 40 were diagnosed as HL (45%) and 22 out 40 were diagnosed as in NHL 55% this finding was comparable with a study done by Kurzrock R. et al [26]. But does not agree with a study done by Yaqo RT. [22] who found that HL patients was about 24% from the cases and NHL was 76%. This can be explained by smaller size of our sample, by different geographic distribution of the cases as well as genetic difference and ethnicity of the population.

By applying Ann-Arbor staging system on the patients of this study show that most of NHL patients were with stage IV disease 72. 7%,18. 2% in stage III and 9. 1% in stage II. This finding does not agree with study done by Pedersen LM et al [27] and Ishtiaq J et al [28], the higher percentage of the patients with stage IV can be explained by the lack of routine checkup which lead to late diagnosis in Iraqi patients, therefore they usually presented with advanced clinical stage.

In this study the percentage of HL patients with stage IV disease was (27. 7%) with stage III (16. 6%) and with stage II (55. 5%), this finding was comparable with a study done by Hohaus S. et al [13] a part from that in the current study there was no patients with stage I disease. The highest percentage of HL patients with stage IV in this study does not agree with a study done by Biggar RJ. et al [25] Nadeem M et al [29] this can be explained by the lack of routine checkup which lead to late diagnosis in Iraqi patients, they usually presented with advanced clinical stage.

Regarding anemia in lymphoma patients,it was found that about 72. 5% of patients were anemic with Hb less than 12, this finding agree with a study done by Ludwig et al [31] and Brigegard G et al [32]. In this study it was found that half of the patients with HL were anemic (50%). This agree with Birgegard G. et al [32] Hohaus S. et al [13]. In this study we found that 90. 9% of patients with NHL was anemic this finding does not agree with study done by Birgegard G. et al [32], Who found that frequency of anemia in NHL patients were 77. 9%, this may be explained by the fact that patients in Iraq usually present in a more advanced stage of the illness due to lack for routine checkup and patients with advanced stage have higher rate of B. M infiltration,which explain the anemia.

In this study we found that B. M. involvement was found in 11 patients and all the patients with B. M. involvement had NHL diagnosis, This finding agree with a study done by Ishtiaq J. et al [28]. In this study the mean level of hepcidin were much higher in lymphoma patients compared to healthy controls this agree with studies done by Hohaus S. et al [13], Biggar RJ et al [25], kurzrock R. et al [26], Guney N. et al [33] and Hara M et al [34].

In this study we found that there is an inverse correlation between hepcidin mean level with Hb level this finding agree with Hohaus S. et al study [13]Ibricevic – balic L. et al [35] Hara M. et al [34], Hassan EA. et al [36] In this study the mean level of hepcidin has positive relation with the stage of the disease (patient with stage IV had higher level of hepcidin than stage III, and stage III higher than stage II), this finding agree with study done by Hara M. et al [33], Hohaus S. et al [13], Patients with advanced stage have higher IL-6 level which induce hepcidin synthesis, this lead to increase hepcidin level in patients with advanced stage.

In this study we found positive relationship between hepcidin level and the presence of B-symptoms this finding agree with Hassan EA. et al [35]. In this study there was no significant correlation between hepcidin level and the presence of bulky disease, patients age, and gender difference, this does not goes with the

finding of Hohaus S. et al [13], this may explained by small size of the sample and lower number of patients who had bulky disease in this study.

From the previous findings we can propose that lymphoma disease activity associated with production and release of cytokines such as IL-6 into the systemic circulation, which stimulate the over production of hepcidin Increased levels of hepcidin in the liver cause a state of functional hypoferremia, which correlates with anemia and contributes to it. The finding that hepicidin level is also elevated in no anemic pt. compared to control group and Future research may examine the relationship between hepcidin and prognosis and whether these associations will disappear following treatment in light of the association between hepcidin and adverse prognostic factors.

Conclusion:

1. Hepcidin level was high in lymphoma patients compare to control.
2. Hepcidin level was significantly higher in lymphoma patients with anemia than not anemic patients
3. Hepcidin play as important role in the development of anemia in lymphoma.
4. The adverse impact of elevated hepcidin is consistent demonstration of higher level of hepcidin in people with B symptoms and advanced stages.

Institutional Review Board Statement:

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of University of Mosul. (K\2\13\136) in 11\6\2023

Informed Consent Statement:

Informed consent was obtained from all subjects involved in the study.

Acknowledgments:

The authors would like to thank the University of Mosul, Iraq.

Funding:

This research did not receive any specific fund.

Conflicts of Interest:

The authors declare no conflict of interest.

References

1. Press, O. W. ; Lichtman, M. A. General Consideration for lymphomas: Epidemiology, etiology, heterogeneity and primary extranodal disease. . In: Kaushansky K, Lichtman MA, Prchal J, et al. Editors. Williams *Haematology*. Ninth Edition. US:McGraw Hill Professional 2015; 11: 1569.
2. Lees, C. ; Keane, C. ; Gandhi, M. K. ; Gunawardana,J. Biology and therapy of primary mediastinal B-cell lymphoma: current status and future directions. *Br J Haematol*. 2019;185(1):25-41.
3. Metzger, M. L. ; Mauz-Körholz,C. Epidemiology, outcome, targeted agents and immunotherapy in adolescent and young adult non-Hodgkin and Hodgkin lymphoma. *Br J Haematol*. 2019 Jun;185(6):1142-1157.
4. Schwock, J. ; Geddie,W. R. Diagnosis of B-cell non-hodgkin lymphomas with small-/intermediate-sized cells in cytopathology. *Patholog Res Int*. 2012;2012:164934. doi: 10. 1155/2012/164934.
5. Gunduz,E. ; Celebioglu, M. ; Meltem AKay, O. The role of flow cytometry in the diagnosis of Non-hodgkins lymphoma, Hodgkins lymphoma, granulomatous inflammation and reactive lymph node specimens. *JBUON*. 2013;18(3):739-45 .
6. Sun, R. ; Medeiros, L. ; Young, K. Diagnostic and predictive biomarkers for lymphoma diagnosis and treatment in the era of precision medicine. *Mod Pathol*. 2016(29): 1118–1142 https://doi. org/10. 1038/modpathol. 2016. 92
7. Paul, T. ; Gautam, U. ; Rajwanshi,A. Flowcytometric immunophenotyping and cell block immunocytochemistry in the

diagnosis of primary Non-hodgkins lymphoma by fine-needle aspiration: Experience from a tertiatry care center. *Jcytol*. 2014 ; 31(3): 123-130.

8. Mani, H. ; Jaffe, E. S. Hodgkin lymphoma: an update on Its biology with new insights into classification. *Clin lymphoma Myeloma*. 2009; 9(3): 206-216.
9. Yasmeen, T. ; Ali, J. ; Khan, K. , Siddiqui, N. Frequency and causes of anemia in Lymphoma patients. *Pak J Med Sci*. 2019;35(1):61-65. doi: 10. 12669/pjms. 35. 1. 91.
10. Hong, J. ; Woo, H. S. ; Kim, H. ; et al. Anemia as useful biomarker in Patients with diffuse large B-cell lymphoma treated with R-CHOP immunochemotherapy. *Cancer Sci*. 2014; 105(12):1569-1575.
11. Briukhovetska, D. , Dörr, J. , Endres, S. *et al*. Interleukins in cancer: from biology to therapy. *Nat Rev Cancer*. 2021(21): 481–499. https://doi. org/10. 1038/s41568-021-00363-z.
12. Kim, Y-J; Kim, K-S; Lim, D. , Yang, D. J. ; Park, J-I; Kim, K. W. ; Jeong J-H, Choi H-S, Kim D-K. Epigallocatechin-3-Gallate (EGCG)-Inducible SMILE Inhibits STAT3-Mediated Hepcidin Gene Expression. *Antioxidants*. 2020; 9(6):514. https://doi. org/10. 3390/antiox9060514.
13. Kroll, M. H. Hematology. Approach to Internal Medicine. 2015 13:159–202. doi: 10. 1007/978-3-319-11821-5_6. PMCID: PMC7123236. .
14. Fernandez – Alvarez, R. , Gonzalez – Rodrigues, A. P. , Gonzalez, M. E. Serum ferritin as prognostic marker in classical Hodgkins Lymphoma treated with ABVD-based therapy. *leuk lymphoma*. 2015
15. Nemeth, E. , Ganz, T. Hepcidin and Iron in Health and Disease. *Annu Rev Med*. 2023 27;74:261-277. doi: 10. 1146/annurev-med-043021-032816.
16. D'Angelo, G. Role of hepcidin in the pathophysiology and diagnosis of anemia. *Blood Res.* 2013;48(1):10-5. doi: 10. 5045/br. 2013. 48. 1. 10. .
17. Katsarou, A. , Pantopoulos, K. Hepcidin Therapeutics. Pharmaceuticals (*Basel)*. 2018 21;11(4):127. doi: 10. 3390/ph11040127.
18. Vela,D. Hepcidin, an emerging and important player in brain iron homeostasis. *J Transl Med*. 2018 (16) 25. https://doi. org/10. 1186/s12967-018-1399-5
19. Georgopoulou, U. ; Dimitriadis, A. ,Fako, P. ; et al. Hepcidin and the iron enigma in HCV infection. *Virulence*. 2014; 5(4): 465-476.
20. Fadhil, M. S. ; Al-Nueimy, W. M. , Lazim, A. F. Hodgkin's lymphoma. An immunohistochemical profile in northern Iraq. *Saudi Med J*. 2014; 35(5): 448-453.
21. Results of Iraqi Cancer Registry 2009, Iraqi Cancer board, Iraqi Cancer Registry Centre, Ministry of Health, Baghdad-Iraq. 2009. 133-148.
22. Yaqo, R. T. ; Hughson, M. D. ; Sulayvani, F. K. , et al. Malignant lymphoma in northern Iraq: a retrospective analysis of 270 cases according to the World Health Organization classification. *Indian J Cancer*. 2011; 48(4):446-451
23. Alwan, A. F. ; Al-Rahal, N. K. ; Shabeeb, Z. A. , et al. Incidence of Epstein Barr Virus infection in newly diagnosed non-Hodgkin lymphoma in the national center of hematology-single center study. *Iraqi Journal of Cancer and Medical Genetics*. 2014; 7: 21-25.
24. Kamil,T. S. ; Al-rawi, R. A. ; Alhaideri M. Immunohistochemical and clinicopathological study of non-Hodgkin's lymphoma in Erbil, Kurdistan. *Zanco J Med Sci*. 2014; 18(2): 756-762.
25. Biggar, R. J. ; Jhonnsen, J. S. ; Smedby, K. E. , et al. Serum YKL-40 and IL-6 Levels in Hodgkin Lymphoma. *Clin Cancer Res*. 2008; 14(21): 6974-6978.

26. Kurzrock,R. ; Redman, J. ; Cabanillas, F. ; et al. Serum IL-6 Are elevated in lymphoma Patients and correlate with survival in Advanced H. D and with B-symptoms. *CANCER RESEARCH*. 1993; 53(9): 2118-2122.
27. Pedersen, L. M. ; Sorensen, P. G. Mediators of inflammation correlate with microalbuminuria in patients with non-hodgkins lymphoma. *British Journal of Haematology*. 2003; 121:275-279.
28. Ishtiaq, J. ; Jehanzeb, K. ; Ali,N. ; et al. Bone Marrow Infiltration and Pattern in Previously diagnosed Patient of non-hodgkin lymphoma(a single center study). *Pak Armed Forces Med J*. 2017; 67 (2): 249-252.
29. Nadeem, M. ; Nagi, N. ; Hussain, I. ; et al. Frequency of Bone Marrow Involvement in Hodgkin's Lymphoma on First Presentation. Journal of the College of Physicians and Surgeons Pakistan. 2009; 19(12): 766-771.
30. Al-Karawi, Abdullah Salim, and Ali Saad Kadhim. "Exploring the role of autoantibodies in Iraqi females with polycystic ovary syndrome. "
31. Ludwig H, Van-Belle S, Barrett-Leep P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer*. 2004;40(15):2293-2306.
32. Birgegard,G. Managing anemia in lymphoma and multiple myeloma. *The Clin Risk Manag*. 2008; 4(2): 527-539.
33. Guney, N. ; Soydin, H. O. ; Basaran, M. ; et al. Serum levels of interlenkin-6 and interlenkin-10 in Turkish Patient with aggressive, non-Hodgkin's lymphoma. *Asian Pac J Cancer Prev*. 2009; 10:669-674.
34. Hara, M. ; Ando, M. ; Tsuchiya, K. ; et al. Serum hepcidin-25 level linked with high mortality in Patients with non-Hodgkin lymphoma. *Ann Hematol*. 2015; 94: 603-608.
35. Ibricevic-balic, L. ; Icindic-Nakas, E. ; Hasic, S. ; et al. Dilemma: Correlation Between Serum Level of Hepcidin and IL-6 in Anemic Myeloma Patients. *Med Arch*. 2016; 70(6): 429–432.
36. Hassan, E. A. ; Kamal, G. M; Sedky, A. M. ; et al. Role of Hepicidin in multiple myeloma and lymphoma Patients. *International Journal of innovative research and development*. 2017; 6(6): 181-186.
37. Alajeeli, F. S. , Al-Karawi, A. S. , & Ali, M. M. (2023). The Immunological Significance of Medicinal Plants in Disease Control and Prevention in Humans. *Al-Salam Journal for Medical Science*, *2*(2), 13-19.
38. Abid, F. M. , Al-Ajeeli, F. S. , Al-Karawi, A. S. , & Rasool, K. H. (2023). Reversed phase HPLC determination of total homocysteine, cysteine, cysteinyl glycine, glutathione in plasma of epileptic patients. *The American Journal of Medical Sciences and Pharmaceutical Research*, *5*(07), 34-45.