Faraj HR. Babcock Univ. Med. J.2025 8(S1):54-59
https://doi.org/10.38029/babcockuniv.med.j..v8iS1.783
eISSN: 2756-4657

RESEARCH ARTICLE OPEN ACCESS

Clinical study of the role of Procalcitonin and some biochemical parameters in patients with Lymphoma in Thi-Qar Province - Iraq

Faraj HR[1]ID

[1]*Department of Chemistry, College of Science, University of Thi-Qar, Thi-Qar, 64001, Iraq*

Submitted: 22nd January 2025
Accepted: 16th April 2025
Published: 30th April 2025
ID: Orcid ID

Abstract
Objective: Lymphoma is a type of cancer that starts in the immune system's lymphocytes, which fight infections. The spleen, thymus, bone marrow, lymph nodes, and other organs contain these cells. When lymphoma occurs, lymphocytes alter and proliferate uncontrollably. This study is one of the initial Iraqi efforts to investigate the serum Procalcitonin, TNF-α, IL-6, and Zinc levels in Lymphoma patients and compare the values with those of healthy controls.
Methods: This study was a case-control study of 43 patients with Lymphoma and 37 controls recruited at the Oncology centre, referring hospitals, private clinic and laboratories in Thi-Qar, province of Iraq. Smokers, alcoholics, and recent antibiotic users were excluded from the study to mitigate the confounding effect. Serum Procalcitonin, TNF-α, IL-6, and Zinc levels were assessed in all participants.
Result: The participants' ages ranged from 17 to 32 years. The mean levels of serum procalcitonin ($p<0.0001$), TNF-α ($p<0.0001$), and IL-6 ($p<0.0001$) levels of patients with Lymphoma were significantly higher than those of the control group. However, serum zinc level was lower among the cases than the control group ($p<0.0001$).
Conclusion: In patients with solid tumours, the combined measurement of PCT and IL-6 may serve as indicators of the progression of neoplastic diseases. Serum TNF-α and IL-6 levels can serve as prognostic indicators for the assessment of tumour immune status in Lymphoma. Poor nutritional status at initial diagnosis may have affected serum zinc levels in lymphoma patients.

Keywords: Lymphoma, Procalcitonin, TNF-α, IL-6, Zinc

Plain English Summary
Lymphoma is a cancer that starts in the lymphatic system, which helps the body fight infections. People with lymphoma often have weakened immune systems and are more at risk of infections and inflammation. This study examined the levels of four substances in the blood- Procalcitonin (PCT), TNF-α, IL-6, and Zinc—in 43 lymphoma patients compared to 37 healthy individuals in Thi-Qar, Iraq. The findings showed that PCT, TNF-α, and IL-6 were significantly higher in patients, indicating increased inflammation and immune activity. Zinc levels, however, were lower, possibly due to poor nutrition or weakened immunity. These results suggest that measuring PCT and IL-6 may help track disease progression, while TNF-α and IL-6 could serve as markers of the immune response in lymphoma. Low zinc levels may also highlight the need for nutritional support in these patients. These biomarkers could help monitor lymphoma progression and guide nutritional support.

Background

The abnormal cell growth of B-cell, T-cell, and natural killer (NK) cell subsets of lymphocytes at various stages of maturity results in lymphomas, a diverse group of cancers (1, 2). A common symptom of lymphoma is painless adenopathy. In more aggressive variants, adenopathy may advance quickly, or it may wax and wane over

Correspondence:
Faraj, Hadeel R
Department of Chemistry, College of Science,
University of Thi-Qar,
Thi-Qar, 64001, Iraq
+9647814252220, hadeal.r_chem@sci.utq.edu.iq

years in indolent presentations. The supradiaphragmatic lymph nodes are the most common site for Hodgkin lymphoma. Although non-Hodgkin lymphoma can develop anywhere in the body, several subtypes have their origins in the skin, central nervous system, or gastrointestinal tract. Individuals with more advanced disease may experience systemic symptoms such as fever, unexplained weight loss, and night sweats. Lymphomas spread to extra-nodal locations in two major ways: direct invasion or hematogenous dissemination to the spleen, liver, lungs, or bone marrow (3, 4, 5).

Procalcitonin (PCT) is the 116-amino pre-hormone of calcitonin that is typically produced by the thyroid's parafollicular C-cells and released into the bloodstream in response to hypercalcemia. Before entering the systemic circulation, the generated PCT is normally nearly completely transformed into its mature form, calcitonin (6, 7, 8). Through a different biologic mechanism, non-thyroid tissue types such the spleen, kidney, liver, pancreas, colon, brain, and lungs may produce PCT, which results in noticeably higher serum PCT levels (9, 10). On the other hand, activated macrophages, T-cells, and natural killer cells are the primary producers of tumour necrosis factor alpha (TNF-α), a pro-inflammatory cytokine that is both soluble and membrane-bound. Although TNF-α has been linked to anticancer properties, it has been discovered that cancer patients' tumour and plasma samples had higher TNF-α receptor levels. This finding has been interpreted as a mechanism of cancer survival to mitigate high levels of cytokines (11). Whereas IL-6 is the cytokine most connected with anaemia (12). It is a multifunctional cytokine that influences the activity of cancer cells" (13).

Zinc is an essential component of transcriptional gene control, cellular differentiation and proliferation, and the catalytic activity of carbonic anhydrase. It is a cofactor for over 200 enzymes in the body (14). Red blood cells have a high quantity of enzymes (15).

Lymphoma patients face significant risk of infections, inflammation, and immune dysfunction, which are critical to management, disease progression and prognosis. Investigating the biochemical indicators of these phenomena is, therefore, vital. Elevated PCT indicates bacterial infections, while TNF-α and IL-6 reflect disease activity and inflammation. Zinc deficiency, on the other hand, may predispose to impaired immunity (16).

The objective of this study is to evaluate the role of serum Procalcitonin (PCT), TNF-α, IL-6, and Zinc in lymphoma patients to assess infection risk, inflammation, and immune dysfunction, which are critical for lymphoma prognosis and treatment. Based on literature, the author hypothesised that PCT, TNF-α, and IL-6 would be elevated, while Zinc would be reduced, in lymphoma patients.

Materials and Methods

Collection of Blood Sample

The investigator obtained 5ml of blood samples from Lymphoma patients and controls and allowed the blood to clot at room temperature in empty disposable tubes. Then, the samples were centrifuged at 3000 xg for ten minutes, and the serum samples were separated and were either stored at -20ºC until use or used immediately to analyse biochemical parameters.

Study Design

This study was designed as a case-control study. All samples were taken from patients who were recruited consecutively among those attending the Oncology Centre in Thi-Qar and other specialist clinics. All diagnosed of all types of lymphoma, irrespective of stage during the study period were recruited. The study participants included 80 subjects, 43 of which were patients with Lymphoma (20 females and 23 males) and 37 (17 females and 20 males), from healthy individuals who served as controls. Controls were recruited from age and sex-matched (to account for demographic influences on immune and inflammatory markers) blood donors (to mitigate selection bias). The controls underwent physical examination and baseline screening to confirm the absence of infections, autoimmune disorders, malignancies, and chronic inflammatory conditions. The study excluded people who had recently been vaccinated, used antibiotics or steroids, were pregnant, smokers or alcoholics to avoid skewing the biomarker levels, especially Zinc and IL-6 (17).

Biochemical Parameters

Serum Procalcitonin, TNF-α, and IL-6 were estimated by enzyme linked immunoassay method by ELISA Reader, USA. Using kits supplied by Elabscience, USA. Serum Zinc was analysed by colourimetric method by UV/VIS spectrophotometer, Japan using kit supplied by Spectrum diagnostics, Germany (18,19). Quality control samples were run in duplicate, with intra- and inter-assay coefficients of variation (CVs) <10% and <15%, respectively, as per manufacturer specifications and CLSI guidelines (EP05-A3).

Statistical Analysis

Statistical analysis was done using the IBM SPSS Software version 20.0. The results were expressed as mean ± standard deviations (mean ± SD). Data normality was confirmed via the

Shapiro-Wilk test. To compare parameters in various study groups, the one-way ANOVA test was performed. P-values ($p \leq 0.05$) were used to determine statistical significance. Pearson correlation coefficients (r) will be used to describe relationships among various parameters within each group.

Results

The participants' ages ranged from 17 to 32 years. The present study included eighty subjects, categorised into two groups: the Lymphoma patients' group, which comprised forty-three patients and the healthy controls group of thirty-seven individuals. The mean ages, Body Mass Index, and sex distribution of the two groups were similar ($p > 0.05$). The characteristic data for all studied groups is shown in Table 1.

Table 1: Details of numbers and age of the groups studied

Groups	N	Age (years) Mean ± SD	BMI (kg/m2) Mean ± SD	Sex (M/F)
Patients	43	26.2 ± 6.1	25.2 ± 5.5	23 /20
Controls	37	25.3 ± 4.2	23.6 ± 3.4	20 / 17
p-value		0.4519	0.1290	0.9596

N: Number of subjects, M: male, F: Female, BMI: body mass index

Table 2 shows the levels of Procalcitonin in patients and controls. In this table, it is observed that there was a significant increase in the levels of serum Procalcitonin in the patient group compared to the control group ($p<0.0001$).

Table 2: Serum levels of Procalcitonin in Lymphoma patients and controls group

Groups	N	Procalcitonin (pg/mL) Mean ± SD	p-value
Patients	43	2110.5 ± 303.4	<0.0001
Controls	37	1033.8 ± 247.1	

Each value represents mean ± SD values with non-identical superscript (a and b) were considered significantly differences ($p \leq 0.05$). N: number of subjects. SD: standard deviation

Table 3 shows the levels of Tumour Necrosis Factor-α and Interleukin – 6 in patients and controls. In this table, it was observed that there was a significant increase in the levels of serum TNF-α and IL- 6 in the patients' group in comparison to the control group ($p<0.0001$).

Table 3: Serum level of TNF-α and IL-6 in Lymphoma patients and controls group

Groups	N	TNF-α (pg/ml) Mean ± SD	IL-6 (pg/ml) Mean ± SD
Patients	43	552.2 ± 44.1	122.3 ± 21.4
Controls	37	391.3 ± 17.98	74.7 ± 11.8
p-value		<0.0001	<0.0001

Each value represents mean ± SD values with non-identical superscript (a and b) were considered significantly differences ($p \leq 0.05$). N: number of subjects. SD: standard deviation

According to Table 4, the serum Zinc concentration of the patients' group was noticeably lower than that of the controls ($p<0.0001$).

Table 4: Serum level of Zinc in Lymphoma patients and controls group

Groups	*N*	Zinc (µmol /L) Mean ± SD	p-value
Patients	43	8.41 ± 1.2	<0.0001
Controls	37	14.9 ± 3.1	

Each value represents mean ± SD values with non-identical superscript (a and b) were considered significantly differences ($p \leq 0.05$). N: number of subjects. SD: standard deviation

Pearson's correlation explains the link between procalcitonin and other parameters in this research. Table 5 reveals a statistically significant positive correlation among procalcitonin, TNF-α, and IL-6. A weak but significant negative correlation ($r = -0.29$, $p = 0.027$) was seen between procalcitonin and Zinc.

Table 5: Correlation between Procalcitonin and other parameters

Procalcitonin versus	r	p-value	Result
TNF-α pg /ml	0.44	0.005	Significant positive correlation
IL-6 pg /ml	0.56	0.012	Significant positive correlation
Zinc µmol /l	- 0.29	0.027	Insignificant negative correlation

Discussion

Tumours of immune cells, lymphomas are solid growths found in lymphoid tissues such lymph nodes and bone marrow. Examples include Hodgkin's and non-Hodgkin's lymphomas (20, 21)**.** It might be difficult to interpret high PCT concentrations in blood in cancer patients because they can be affected by several factors, including the presence of metastases or the neuroendocrine activity of malignant tissue (e.g., small-cell lung cancer). In these situations, there may be an increase in PCT concentrations independent of infections, indicating a low specificity for bacterial infections (21). Patients with widespread metastatic illness have reported contradictory PCT concentrations. According to previous studies (22, 23). PCT levels were much higher in patients with solid tumours and metastases with no signs of infection, particularly in those with broad metastatic illness. According to other scientists, PCT might be a useful early predictor of neoplastic disease development (23).

TNF-α is mostly produced in peripheral tissues and/or adipocytes, and it causes tissue-specific inflammation by activating many transcriptional-mediated pathways and generating reactive oxygen species (24, 25). Cytokines such as TNF-α, IL-6, IL-8, and IL-10 have a close immunological connection with lymphoid cells, and their aberrant expression has been related to the poor prognosis of NHL (26). An important part of the lymphoma microenvironment, IL-6 is a powerful cytokine that stimulates the growth and differentiation of B lymphocytes. It also causes angiogenesis in tumours, interferes with tumour cell adhesion, and strongly inhibits the body's antitumor effects, thereby encouraging tumour cell growth and proliferation while preventing apoptosis and starting a vicious cycle (27, 28). Although the specifics of this mechanism are still understood, tumour-induced expenditure and a decline in nutritional status may lower serum zinc levels in malignant tumours. Zinc depletion in lifestyle disorders, ageing, and carcinogenic processes can be caused directly or indirectly by active oxygen. Ninety per cent of diseases are caused by active oxygen, and zinc is a potent, active oxygen-inhibiting component. The active core of superoxide dismutase, an active oxygen-scavenging enzyme, is linked to metals like Cu, Zn, Mn, Fe, and Se. Prior research has demonstrated a correlation between zinc deficiency and low T-lymphocyte counts in patients with head and neck cancer (29, 30). A zinc deficit causes the thymus and bone marrow to produce fewer T and B cells, which makes the body more vulnerable to infection and erodes its defences (31, 32).

The study findings are limited by the absence of exploration of lymphoma subtypes and potential confounders. Future studies must investigate these issues.

Conclusion

Blood PCT evaluation may be highly beneficial for the treatment of cancer patients who are prone to recurrent infections. PCT and IL-6 measurements taken together may even be utilised as markers for the advancement of neoplastic disorders in patients with solid tumours. In lymphoma, serum TNF-α and IL-6 levels can be used as prognostic markers to evaluate the tumour's immunological state. Additionally, they may serve as potential predictors of the prognosis of lymphoma and serve as a foundation for the targeted therapy's development and direction. Other trace elements like iron and copper were not measured. Nonetheless, this study suggests a link between zinc and malignant lymphoma. Serum zinc levels in lymphoma patients may have been impacted by their poor nutritional state at the time of diagnosis. Routine Zinc supplementation may benefit malnourished lymphoma patients. Also, longitudinal tracking of biomarkers during treatment is warranted.

List of Abbreviations

ANOVA: Analysis of Variance
BMI: Body Mass Index
ELISA: Enzyme-Linked Immunosorbent Assay
IL-6: Interleukin-6
NK cells: Natural Killer cells
pg/ml: Picograms per millilitre
PCT: Procalcitonin
SD: Standard Deviation
SPSS: Statistical Package for the Social Sciences
TNF-α: Tumour Necrosis Factor-alpha
µmol/l: Micromoles per Litre
UV/VIS: Ultraviolet/Visible (Spectrophotometer)

Declarations

Ethical approval and consent to participate

This study was designed and conducted in strict compliance with internationally recognised ethical standards for medical research involving

human participants. Before commencing the study, ethical approval was secured from the Institutional Review Board (reference number 91/2023, dated March 13, 2023), ensuring that all procedures met established guidelines for participant safety and scientific integrity.
All enrolled participants provided written informed consent after receiving comprehensive explanations about the study's purpose, procedures, potential risks, and benefits. For participants under 18 years of age, written consent was obtained from parents or legal guardians. We implemented rigorous measures to protect participant confidentiality, including the anonymisation of all collected data and secure storage protocols that restricted access to authorised research personnel only.

Consent for publication
All the authors gave consent for the publication of the work under the Creative Commons Attribution- Non-Commercial 4.0 license.

Availability of data and materials
The data and materials associated with this research will be made available by the corresponding author upon reasonable request.

Competing interests
The authors declare that they have no competing interests.

Funding
Nil.

Author contributions
The author was responsible for all aspects of the study and approved the final version of the paper.

Acknowledgement
Not applicable.

References

1. Mugnaini EN, Ghosh N. Lymphoma. Prim Care. 2016 Dec;43(4):661-675. https://doi.org/10.1016/j.pop.2016.07.012
2. Matasar MJ, Zelenetz AD. Overview of lymphoma diagnosis and management. Radiol Clin North Am. 2008 Mar;46(2):175-98, vii. https://doi.org/10.1016/j.rcl.2008.03.005
3. Ansell SM. Non-Hodgkin lymphoma: diagnosis and treatment. Mayo Clin Proc. 2015;90(8):1152-1163. https://doi.org/10.1016/j.mayocp.2015.04.025
4. Ansell SM. Hodgkin lymphoma: diagnosis and treatment. Mayo Clin Proc. 2015;90(11):1574-1583. https://doi.org/10.1016/j.mayocp.2015.07.005
5. Lewis WD, Lilly S, Jones KL. Lymphoma: diagnosis and treatment. American family physician. 2020 Jan 1;101(1):34-41.
6. Covington, E.W.; Roberts, M.Z.; Dong, J. Procalcitonin Monitoring as a Guide for Antimicrobial Therapy: A Review of Current Literature. Pharmacotherapy 2018, 38, 569–581. https://doi.org/10.1002/phar.2112
7. Becker KL, Nylén ES, White JC, Müller B, Snider RH. Clinical Review 167: Procalcitonin and the Calcitonin Gene Family of Peptides in Inflammation, Infection, and Sepsis: A Journey from Calcitonin Back to Its Precursors. J. Clin. Endocrinol. Metab. 2004, 89, 1512–1525. https://doi.org/10.1210/jc.2002-021444
8. Maruna P, Nedělníková K, Gürlich R. Physiology and Genetics of Procalcitonin. Physiol. Res. 2000, 49 (Suppl. S1), S57–S61.
9. Lippi G, Sanchis-Gomar F. Procalcitonin in Inflammatory Bowel Disease: Drawbacks and Opportunities. World J. Gastroenterol. 2017, 23, 8283–8290. https://doi.org/10.3748/wjg.v23.i47.8283
10. Soreng, K, Levy HR. Procalcitonin: An Emerging Biomarker of Bacterial Sepsis. Clin. Microbiol. Newsl. 2011, 33, 171–178. https://doi.org/10.1016/j.clinmicnews.2011.10.004
11. Mozas P, Rivas-Delgado A, Rivero A, Dlouhy I, Nadeu F, Balagué O, González-Farré B, Baumann T, Giné E, Delgado J, Villamor N. High serum levels of IL-2R, IL-6, and TNF-α are associated with higher tumor burden and poorer outcome of follicular lymphoma patients in the rituximab era. Leukemia research. 2020 Jul 1;94:106371.. https://doi.org/10.1016/j.leukres.2020.106371
12. Casasnovas RO, Monnier N, Brice P, Pauline Brice, Marine Divine, Franck Morschhause, et al . Plasma Cytokine and Soluble Receptor Signature Predicts Outcome of Patients With Classical Hodgkin's Lymphoma. Journal of Clinical Oncology. 2007; 25: 1732-40. https://doi.org/10.1200/JCO.2006.08.1331
13. Guo Y, Xu F, Lu T, Duan Z, Zhang Z. Interleukin6 signaling pathway in targeted therapy for cancer. Cancer Treatment Reviews. 2012; 38(7):904-10. https://doi.org/10.1016/j.ctrv.2012.04.007
14. Guiton AC, Hall JE. Textbook of Medical Physiology. 11th ed. Japanese edition copyright: Elsevier Japan KK; 2010: 925–31.
15. Prasad AS, Halsted JA, Nadimi M. Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism,

dwarfism and geophagia. Am J Med 1961; 31: 532–46. https://doi.org/10.1016/0002-9343(61)90137-1
16. Schuetz P, Birkhahn R, Sherwin R, Jones AE, Singer A, Kline JA, Runyon MS, Self WH, Courtney DM, Nowak RM, Gaieski DF. Serial procalcitonin predicts mortality in severe sepsis patients: results from the multicenter procalcitonin Monitoring Sepsis (MOSES) study. Critical care medicine. 2017 May 1;45(5):781-9. https://doi.org/10.1097/CCM.0000000000002321
17. Quinche F. WHO, Handbook for good clinical research Practice (GCP)(2005), Guidance for implementation.
18. Elabscience. ELISA kit protocols: human Procalcitonin (PCT), TNF-α, and IL-6 [Internet]. Houston (TX): Elabscience; 2023 [cited 2024 Jan]. Available from: https://www.elabscience.com
19. Clinical and Laboratory Standards Institute (CLSI). Evaluation of precision of quantitative measurement procedures; approved guideline. 3rd ed. CLSI document EP05-A3. Wayne (PA): CLSI; 2022.
20. Doan T, Melvold R, Viselli S, Waltenbaugh C. Lippincott's Illustrated Reviews: Immunology, Lippincott Williams & Willins. a Wolters Kluwer business. 2008;336.
21. Shereen J K Al Ali. Estimation of Immunoglobulins and complement component C3 and C4 in some patients with Hodgkin and Non-Hodgkin Lymphoma in Basrah Governorate, University of Thi-Qar Journal of Science (UTJSCI), 2010, 2(3): 48-56.
22. Patout M, Salaun M, Brunel V, Bota S, Cauliez B, Thiberville L. Diagnostic and prognostic value of serum procalcitonin concentrations in primary lung cancers. Clin Biochem. 2014;47(18):263–267. https://doi.org/10.1016/j.clinbiochem.2014.09.002
23. Matzaraki V, Alexandraki KI, Venetsanou K, Piperi C, Myrianthefs P, Malamos N, Giannakakis T, Karatzas S, Diamanti-Kandarakis E, Baltopoulos G. Evaluation of serum procalcitonin and interleukin-6 levels as markers of liver metastasis. Clinical biochemistry. 2007 Mar 1;40(5-6):336-42. https://doi.org/10.1016/j.clinbiochem.2006.10.027
24. Akash MSH, Rehman K, Liaqat A. Tumor Necrosis Factor-Alpha: Role in Development of Insulin Resistance and Pathogenesis of Type 2 Diabetes Mellitus. Journal of Cellular Biochemistry, 2018;119(1):105–110. https://doi.org/10.1002/jcb.26174
25. Qaiser IM, Mahdi MTh, Hamid JA. Evaluation of leptin hormone and Tumor necrosis factor levels in patients with type two diabetes mellitus. University of Thi-Qar Journal of Science (UTJSCI), 2023, 10(1): 96 – 100. https://doi.org/10.32792/utq/utjsci/v10i1(SI).980
26. Dlouhy I, Filella X, Rovira J, Magnano L, Rivas-Delgado A, Baumann T, Martínez-Trillos A, Balagué O, Martínez A, González-Farre B, et al. High serum levels of soluble interleukin-2 receptor (sIL2-R), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF) are associated with adverse clinical features and predict poor outcome in diffuse large B-cell lymphoma. Leuk Res. 2017;59:20–5. https://doi.org/10.1016/j.leukres.2017.05.014
27. Peng X, Shi J, Sun W, Ruan X, Guo Y, Zhao L, Wang J and Li B: Genetic polymorphisms of IL-6 promoter in cancer susceptibility and prognosis: A meta-analysis. Oncotarget. 9:12351–12364. 2018. https://doi.org/10.18632/oncotarget.24033
28. Narazaki M, Tanaka T and Kishimoto T: The role and therapeutic targeting of IL-6 in rheumatoid arthritis. Expert Rev Clin Immunol. 13:535–551. 2017. https://doi.org/10.1080/1744666X.2017.1295850
29. Prasad AS, Beck FW, Grabowski SM, Kaplan J, Mathog RH. Zinc deficiency: changes in cytokine production and T-cell subpopulations in patients with head and neck cancer and in noncancer subjects. Proc Assoc Am Physicians 1997; 109: 68–77.
30. Sangthawan D, Phungrassami T, Sinkitjarurnchai W. Effects of zinc sulfate supplementation on cell-mediated immune response in head and neck cancer patients treated with radiation therapy. Nutr Cancer 2015; 67: 449–56. https://doi.org/10.1080/01635581.2015.1004735
31. Rink L, Kirchner H. Zinc-Altered Immune Function and Cytokine Production. J. Nutr. 2000, 130, 1407S–1411S. https://doi.org/10.1093/jn/130.5.1407S
32. Chavakis T, May AE, Preissner KT, Kanse SM. Molecular mechanisms of zinc-dependent leukocyte adhesion involving the urokinase receptor and beta2-integrins. Blood 1999, 93, 2976–2983. https://doi.org/10.1182/blood.V93.9.2976