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Effect of Chemotherapy on hs- C Reactive Protein, Some Blood Picture and Kidney Function in Patients With Neuroblastoma

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***Abstract*— Background: Neuroblastoma, the most common extra-cranial malignant pediatric solid tumor and one with a high mortality rate. Children suffering from Neuroblastoma after chemotherapy suffer from anemia, severe infections, and effects on some organs of the body. Therefore, the current study aims to study the effect of chemotherapy on inflammatory factor (high-sensitivity C - reactive protein), some hematological parameters such as white blood cells, platelets, and hemoglobin, and some kidney function such as urea and Creatinine in children with Neuroblastoma before and after three cycles of chemotherapy.**

Materials and methods: 70 cases were divided into three groups: Group A; 35 healthy children are included as a control group., and group B; consists of 35 newly diagnosed patients and group C; following three chemotherapy rounds (same patients newly diagnosed), with an age range from 2 months to 12 years. They had attended Basrah Specialist Hospital for Children from May 2022 to the end of March 2023. Results: When compared to the control group, the results of the current study showed a significant rise ($p \leq 0.05$) in the levels of high-sensitivity C-reactive protein, white blood cells, and platelets in the sera samples of patients with Neuroblastoma, before chemotherapy. When compared to the control group, the results demonstrated that the levels of hemoglobin in the sera samples of patients with Neuroblastoma before chemotherapy had decreased statistically significantly ($p \leq 0.05$). On the other hand, the data showed decreased levels, in each of the following parameters in Neuroblastoma patients after receiving three chemotherapeutic doses: body mass index, white blood cells, and platelets, while that levels of high-sensitivity C-reactive protein remain constantly rising after chemotherapy, whereas hemoglobin levels remain constantly low after treatment, whereas Creatinine and urea levels remain as they were at the time of diagnosis.

Conclusion: This study came to the conclusion that Neuroblastoma treatment considerably changed a number of hematological markers and hs-crp. Consequently, it is essential to monitor these signs.

Keywords— Neuroblastoma, chemotherapy, hs-CRP, kidney function test, CBC.

I. INTRODUCTION

Cancer is a dangerous, life-threatening disorder that affects children, despite being rare among them. Numerous studies have demonstrated that parental exposure to diverse environmental variables may have an effect on the development of malignancies in children, despite the fact that the precise etiology of cancer is still unclear. Pollution, pesticides, and cigarette smoke are potential environmental variables in the parents' home [1]. Malnourished children with cancer are more prone to infection. Using anthropometric indices, such as height, weight, and body mass index (BMI), one can typically evaluate a child's growth status and body composition [2]. Since the tumor-associated inflammatory response in the tumor microenvironment promotes carcinogenesis and tumor development, inflammation is recognized as one of the features of cancer [3]. High-sensitivity C-reactive Protein (hs-CRP) an acute-phase plasma protein that elevates during systemic inflammation, is one of the most often used inflammatory indicators [4]. By activating complements, binding to monocyte receptors, and secreting lymphokines, it can take part in the inflammatory response. The amount of the infection in the human body increases with its levels [5]. Despite the fact that this illness has been treated with cutting-edge medications such as surgery, chemotherapy, radiation, myeloablative consolidation treatment with stem cell rescue or transplantation, and immunotherapy, many patients still have poor prognoses [6]. Endogenous metabolic waste products as well as medications and toxins are eliminated by the kidneys. Many chemicals, particularly those used in oncology, have nephrotoxic effects, they expose them to harm [7], and so urea and creatinine were measured. The properties of a complete blood count (CBC) might be priceless tools [8]. Previous research has shown that the CBC components can be used to predict the risk of cancer, type 2 diabetes (T2DM), arteriosclerosis, cardiovascular disease (CVD), and metabolic syndrome.

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When assessing acute or chronic infections, CBC levels are employed [9]. The reason for our conducting this study is due to the prevalence of childhood cancer in the southern region of Iraq, especially Basra Governorate, due to environmental pollution resulting from the burning of oil and other pollutants, in addition to the remnants of war. Moreover, due to the lack of studies that study solid tumors, especially neuroblastoma therefore, this study was conducted to find out the changes that the tumor may cause in the body and the effect of chemotherapy after three cycles of treatment on the BMI, hs-CRP, WBCs, Hb, and PLT.

II. Materials and Methods

Seventy research participants, children (boys and girls), were included to take part in the current study from May 2022 to March 2023 at the Al-Basrah Children's Teaching Specialty Hospital of south Iraq in the Basra Governorate. The 70 children in this study range in age from 2 months to 12 years. They were split into three groups:

Group A: 35 healthy children are included as a control group.

Group B: consists of 35 newly diagnosed patients.

Group C: following three chemotherapy rounds (same patients as before chemotherapy).

The diagnosis was achieved clinically by the specialists and have done some routine blood tests for patients.

Written informed consent was obtained from the parents of the sick children.

Patients with diabetes and autism spectrum disorders were excluded.

A quantity of six milliliters of intravenous blood samples were collected from healthy subjects and the patients, the blood samples were divided into two part. The first part was collected in EDTA tubes. The second part of blood samples were also collected in gel tubes, then left for half an hour and centrifuged for 15 minutes at 3000 rpm, the serum samples were separated and stored at (-20 ºC) for later measurement of biochemical parameters, unless used immediately.

The serum was used for the estimation of Urea. it was measured according to the method of Talke and Schubert [10]. Creatinine (Cr)was measured according to the method of Bartels et al [11]. The urea reagents used were supplied by Biolabo, France. The Creatinine reagents used were supplied by Randox, France. ELISA (Enzyme Linked Immunosorbent Assay) was also used to measure hs-CRP. Additionally, CBC tests were performed using the ABX Micros ES 60/US to measure the number of blood cells in the circulating blood.

III. Statistical Analysis

Results of the statistical analysis were expressed as the mean standard deviation using the statistical analysis for the social sciences version 23. T test was used to compare parameters across all studied groups. P-values ($P \leqslant 0.05$) were considered.

IV. Result

Table (1) provides a summary of the general characteristics of the children who took part in the study, which include the following details on Smoking Parents and Polluted Residential Areas.

Table 1: Clinical Characteristics of the Studied Groups.

Clinical Characteristics	Percentage	
Smoking Parents	Yes	16 (45.7 %)
	No	19 (54.3 %)
Polluted Residential Areas	Yes	12 (34.3 %)
	No	23 (65.7 %)
Total	……..	35 (100 %)

The results showed an increase in BMI in patient groups before chemotherapy in comparison with control groups ($p \leqslant 0.05$), while a decrease in BMI in patient groups after 3 cycles of chemotherapy in comparison with pre group ($p \leqslant 0.05$), as shown in table (2) and figure (1).

Table 2: BMI for patient and control groups.

Groups	NO.	BMI(Kg/m^2) Mean ±SD
A	35	14.59±4.23 ^{b}
B	35	15.32±3.53 ^{a}
C	35	11.86±3.62 ^{c}

BMI (kg/m²) = weight (kg)/height (m²).

A: control, B: Before chemotherapy, C: after chemotherapy. SD represents the Standard deviation. No represents the Number of subjects. LSD represents the Least Significant Difference (a, b, c) indicates having various letters in same column have been significantly differed (P <0.050).

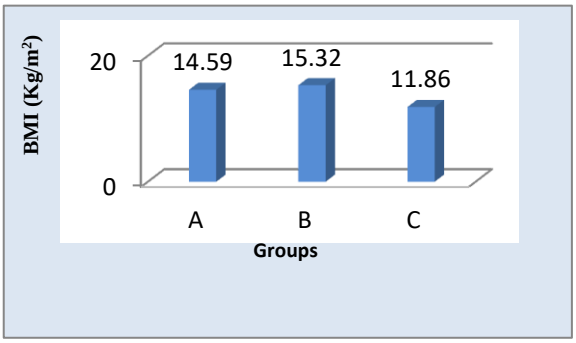

Fig. 1.BMI in patient and control groups.

The table (3) and figure (2) show a significant increase in the concentration of hs-CRP in C group in comparison with A and C groups ($p \leqslant 0.05$). It was found a significant increase in the concentration of hs-CRP in B group in comparison with group A ($p \leqslant 0.05$).

Table 3: Levels of serum hs-CRP in patient and control groups.

Groups	No.	hs-CRP (Mean ±SD)
A	35	1.62 ± 0. 36 [c]
B	35	41.5 ±9.38 [b]
C	35	50.10±9.40 [a]
L.S.D		2.43

Legend as in Table 2.

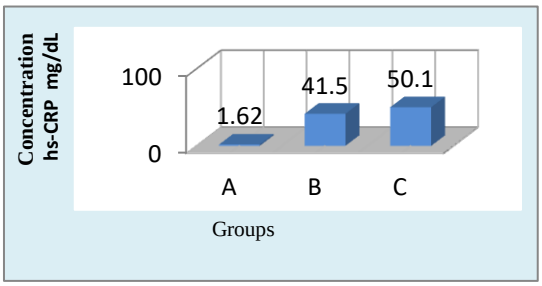

Fig. 2. Levels of serum hs-CRP in patient and control groups.

Table (4) and figure (3) show no significant deference in the concentration of urea between all study groups (p≤ 0.05).

Table 4: Levels of serum urea and Cr in patient and control groups.

Groups	No.	Urea (mmol/L) (Mean ±SD)	Cr (µmol/L) Mean ± SD
A	35	2.69 ±0.92 [a]	35.79 ± 5.05 [a]
B	35	2.76 ±0.79 [a]	36.16 ± 4.22 [a]
C	35	2.79 ±0.71 [a]	35.02 ± 7.61 [a]
L.S.D		0.32	2.30

Legend as in Table 2.

The same table (4) and figure (4) show no significant deference in the concentration of Creatinine (Cr) between all study groups (p≤0.05).

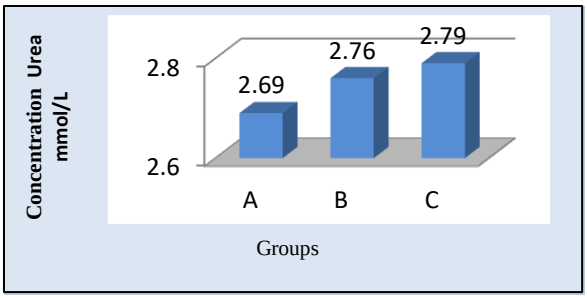

Fig. 3. Levels of serum urea in patient and control groups.

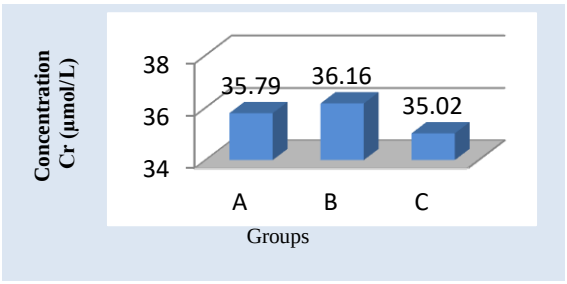

Fig. 4. Levels of serum Cr in patient and control groups.

Table (5) and figure (5) show a significant increase in the level of white blood cells (WBC) in B group in comparison with A and C groups (p≤0.05). It was found a significant increase in the level of WBC in C group in comparison with A group (p≤0.05).

The same table (5) and figure (6) show a significant increase in the level of platelet (PLT) in B group in comparison with A and C groups (p≤0.05). It was found a significant increase in the level of Platelets (PLT) in C group in comparison with A group (p≤0.05).

Also the same table (5) and figure (7) show a significant decrease in the concentration of hemoglobin (Hb) in C group in comparison with A and B groups (p≤ 0.05). It was found a significant decrease in the concentration of Hb in B group in comparison with A group (p≤0.05).

Table (5): Levels of WBC, PLT and Hb in patient and control groups.

Groups	No.	WBC (10 ^3 /UL) (Mean ±SD)	PLT (10 ^3 /UL) (Mean ±SD)	Hb (Mean ±SD)
A	35	4.59±0.97 c	285.83±66.00 c	12.45±0.85 a
B	35	13.16±2.42 a	498.17±98.03 a	9.69±1.32 b
C	35	7.15±1.43 b	398.19±82.87 b	7.91±2.05 c
L.S.D		0.65	33.11	0.62

Legend as in Table 2.

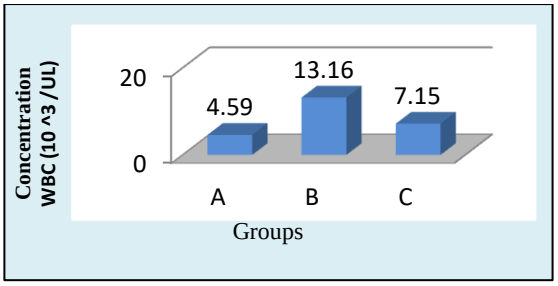

Fig. 5. WBCs Values of patient and control groups.

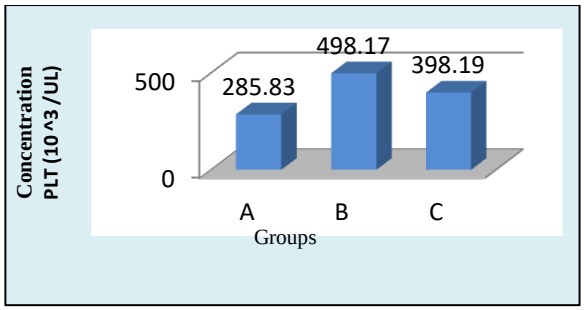

Fig. 6. PLT Values of patient and control groups.

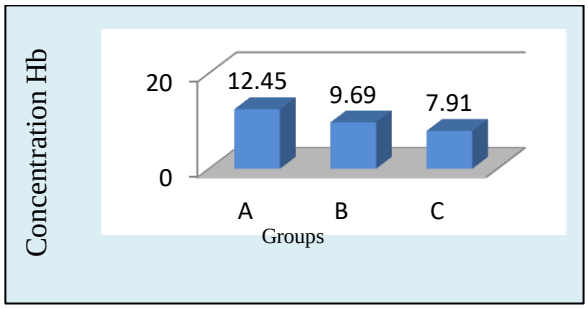

Fig. 7. Hb Values of patient and control groups.

V. DISCUSSION

Children in particular frequently lack the ability to communicate illness symptoms for prompt medical exams. As a result, a significant majority of individuals have advanced disease when they get a diagnosis. Numerous studies have established associations between NB and inflammation [12]. Depending on the period of chemotherapy, patients were split into two groups for this study. Serum values (hs-CRP, urea, Cr, WBC, PLT, and Hb) before and after the chemotherapy treatment were examined in this study.

During therapy, children with NB frequently have low BMIs, due to the negative effects of multimodal therapy as well as the metabolic effects of the tumor. This result may be a reflection of the challenges of providing enough calories to children with cancer. Both short- and long-term negative effects are associated with insufficient energy intake during the treatment of pediatric cancer. In addition to slower growth, it has also been shown that there are cognitive, motor, and neurodevelopmental deficits, decreased tolerance to chemotherapy, and increased susceptibility to infections [13].

According to our findings, cancer patients had much higher levels of hs-CRP than did healthy individuals, which is a marker of a strong inflammatory response. By activating complements, binding to monocyte receptors, and secreting lymphokines, it can contribute to the inflammatory response. The intensity of the infection influences its level in the human body [5]. Furthermore, these results imply that high hs-CRP levels may play a role in the pathogenesis of cancer. This result confirms the theory put out by Lee et al. that chronic low-grade systemic inflammation raises the likelihood of developing cancer [4]. Further, hs-CRP levels increased after chemotherapy treatment. Because chemotherapy is non-specific, it can cause significant tissue damage depending on the dose and course of therapy because it kills both healthy and malignant cells [14].

With respect to the serum urea and Cr levels, there were no appreciable differences in NB patients before, after chemotherapy and control groups; there was a little rise after chemotherapy, but it was not appreciable. This suggests that chemotherapy is not immediately tubulotoxic. Its glomerular side effects are often not clinically significant. These findings were in line with those of Hempel et al.[15], who discovered no appreciable variations in blood urea and Cr levels between ALL patients and the control group.

While the WBC count in patients before chemotherapy was noticeably greater than in control groups, because abnormal WBC production is a key predictor of the existence of leukocytosis, particularly during inflammation, hematological conditions, and solid tumors, where the quantity of WBCs is proven to be a crucial indicator of general health [16]. A high WBC count in blood samples from NB patients is consequently associated to the abundance of lymphoblasts because of the impairment in the growth and development of lymphoid progenitors in the bone marrow, and the increase in leukocyte productivity is typically caused by an increase in the numbers of lymphocytes and neutrophils in the whole blood [17]. Although the WBC count is statistically lower after chemotherapy than it was before chemotherapy. The chemotherapy-induced suppression of hematopoietic stem cells, which are crucial for WBC proliferation, may be the cause of the WBC count reduction in the after chemotherapy period [18]. Therefore, if there is a robust response to treatment, it is likely that there was a noticeable fall in WBC counts after periods of chemotherapy and they may return gradually to normal levels after treatment [19].

Additionally, a substantial decrease in PLT count was seen post-chemotherapy compared to pre-chemotherapy treatment. The reduction in platelet count following therapy may be caused by the chemotherapy-induced destruction of megakaryocytic progenitors during the early phases of differentiation. Failure of megakaryocytic maturation and hence platelet formation, excessive platelet consumption after release into the circulation, or platelet sequestration in an enlarged spleen are the three possible pathways that might cause a lower platelet count [20].

Before chemotherapy hemoglobin levels decreased statistically significantly compared to the control group. Due to several soluble molecules that tumor cells are known to produce and secrete, including tumor necrosis factor, interferon gamma, and interleukin-1, they may be able to lower hemoglobin levels through hemolysis, suppression of erythropoiesis, and impairment of the erythropoietin response of erythroid medullary precursors. This theory states that anemia ought to be viewed as a type of paraneoplastic syndrome, an epiphenomenon reflecting the biologic aggressiveness of cancer [21].

Cancer patients who have anemia may experience a variety of symptoms affecting practically every organ. Dizziness, dyspnea, palpitations, anorexia, and trouble concentrating are examples of less severe symptoms. Lethargy and heart failure are examples of more severe symptoms. One of the most frequent symptoms experienced by cancer patients is fatigue, which may negatively impact patients' quality of life (QOL) [22].

Additionally, post-chemotherapy hemoglobin levels decreased statistically significantly compared to pre-chemotherapy. Cancer patients frequently develop anemia, either as a result of a tumor-driven blood disorder or as a side effect of chemotherapy. Whereas the antineoplastic therapy itself may be a significant contributor to anemia or conversely, may make the patients' pre-existing anemia worse [23].

VI. LIMITATIONS OF THE STUDY

There are some limitations to our study:

First: this was a single-center retrospective study with a relatively small study population, which may lead to selection bias, so large-scale multicenter prospective studies are required to further strengthen the conclusions of this study.

Second: due to the treatment period, there may be a degree of fluctuation at different times of the cycle of treatment. Therefore, measurements must be taken at the end of each session to support the conclusions of this study.

Third: there may be differences in patient treatments on the basis of the treatment guidelines, which may lead to a certain bias.

VII. CONCLUSION

This study concluded that BMI, hs-CRP, and hematological parameters were significantly affected by the NB treatment, while, both before and after chemotherapy, the levels of urea and Creatinine stay the same. Therefore, proper patient follow-up is crucial. To support the results of this study, it is crucial to undertake additional prospective investigations.

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

REFERENCES

[1] Y. Koga *et al*., "Infantile neuroblastoma and maternal occupational exposure to medical agents," Pediatr. Res., no. April, pp. 1–5, 2021, doi: 10.1038/s41390-021-01634-z.

[2] A. J. Murphy, M. White, and P. S. W. Davies, "Body composition of children with cancer," *Am. J. Clin. Nutr.*, vol. 92, no. 1, pp. 55–60, 2010.

[3] A. Winther-Larsen, N. Aggerholm-Pedersen, and B. Sandfeld-Paulsen, "Inflammation-scores as prognostic markers of overall survival in lung cancer: a register-based study of 6,210 Danish lung cancer patients," *BMC Cancer*, vol. 22, no. 1, pp. 1–10, 2022.

[4] S. Lee, J. W. Choe, H. K. Kim, and J. Sung, "High-sensitivity C-reactive protein and cancer," *J. Epidemiol.*, vol. 21, no. 3, pp. 161–168, 2011.

[5] Y. Zhou *et al*., "Clinical effectiveness of matrine sitz bath in treating perianal infection after chemotherapy for acute leukemia," Ann. Cardiothorac. Surg., vol. 9, no. 3, pp. 1109–1116, 2020, doi: 10.21037/apm-20-912.

[6] C. Qi *et al*., "The prognostic value of the advanced lung cancer inflammation index (ALI) for patients with neuroblastoma," J. Int. Med. Res., vol. 50, no. 6, 2022, doi: 10.1177/03000605221109382.

[7] J. Jagieła, P. Bartnicki, and J. Rysz, "Nephrotoxicity as a complication of chemotherapy and immunotherapy in the treatment of colorectal cancer, melanoma and non-small cell lung cancer," *Int. J. Mol. Sci*., vol. 22, no. 9, pp. 1–17, 2021.

[8] L. Agnello, R. Giglio, G. Bivona, C. Scazzone, C. Gambino, A. Iacona, A. Ciaccio, B. Sasso, and M. Ciaccio,
"The value of a complete blood count (Cbc) for sepsis diagnosis and prognosis," *Diagnostics*, vol. 11, no. 10, pp. 1–19, 2021.

[9] I. H. Seo and Y. J. Lee, "Usefulness of Complete Blood Count (CBC) to Assess Cardiovascular and Metabolic Diseases in Clinical Settings: A Comprehensive Literature Review," *Biomedicines*, vol. 10, no. 11, 2022.

[10] H. Talke, G. Schubert, Klin. *Wochschr*., 19, (1965), 43, p.174.

[11] H. Bartels and M. Bohmer, *Clin. Chem*. Acta. 1972, .37: 193.

[12] C. Zheng, S. Liu, J. Feng, and X. Zhao, "Prognostic value of inflammation biomarkers for survival of patients with neuroblastoma," *Cancer Manag. Res*., vol. 12, pp. 2415–2425, 2020.

[13] A. G. Small *et al*., "Neuroblastoma, body mass index, and survival: a retrospective analysis," Med. (United States), vol. 94, no. 14, pp. 1–6, 2015, doi: 10.1097/MD.0000000000000713.

[14] P. Nabapally, "Study on the Levels of CRP Among the Cancer Patients Before and After Chemotherapy Treatment," Indian J. Res., vol. 5, no. 8, pp. 88–89, 2016.

[15] L. Hempel *et al*., "Influence of high-dose methotrexate therapy (HD-MTX) on glomerular and tubular kidney function," Med. Pediatr. Oncol., vol. 40, no. 6, pp. 348–354, 2003, doi: 10.1002/mpo.10293.

[16] M. E. Scheurer *et al*., "An overview of disparities in childhood cancer: Report on the Inaugural Symposium on Childhood Cancer Health Disparities, Houston, Texas, 2016," Pediatr. Hematol. Oncol., vol. 35, no. 2, pp. 95–110, 2018.

[17] Ministry of health, Iraqi Cancer Board. (2017): Results of Iraqi Cancer Registry 2017.
[18] B. Wondimneh, S. A. D. Setty, G. G. Asfeha, E. Belay, G. Gebremeskel, and G. Baye, "Comparison of hematological and biochemical profile changes in pre- and post-chemotherapy treatment of cancer patients attended at ayder comprehensive specialized hospital, mekelle, northern ethiopia 2019: A retrospective cohort study," *Cancer Manag. Res*., vol. 13, pp. 625–632, 2021.
[19] Z. Aljoubouri, "A Physiological and Biochemical Study of Acute Lymphoblastic Leukemia in Iraqi Children before and after Chemotherapy", Ph.D. Thesis in Zoology, Dept. of Biology/ College of Education for Pure Sciences/ University of Karbala, PP. 246, 2021
[20] S. Anoar, "Effect of chemotherapy on vitamin B12, folic acid and some biochemical factors on leukemia (chronic myeloid leukemia) in Iraqi patients". PhD. Thesis, Dept., of Biology/ College of Education Ibn Al-Haitham/ University of Baghdad, Pp:104. 2006.
[21] M. Di Maio *et al*., "The prognostic role of pre-chemotherapy hemoglobin level in patients with ovarian cancer," Front. Biosci., vol. 11, pp. 1585–1590, 2006.
[22] H. Abdel-Razeq and H. Hashem, "Recent update in the pathogenesis and treatment of chemotherapy and cancer induced anemia," *Crit. Rev. Oncol. Hematol*., vol. 145, no. August 2019, p. 102837, 2020.
[23] S. Vignjević Petrinović, A. Jauković, M. Milošević, D. Bugarski, and M. Budeč, "Targeting Stress Erythropoiesis Pathways in Cancer," *Front. Physio*l., vol. 13, no. May, pp. 1–14, 2022.