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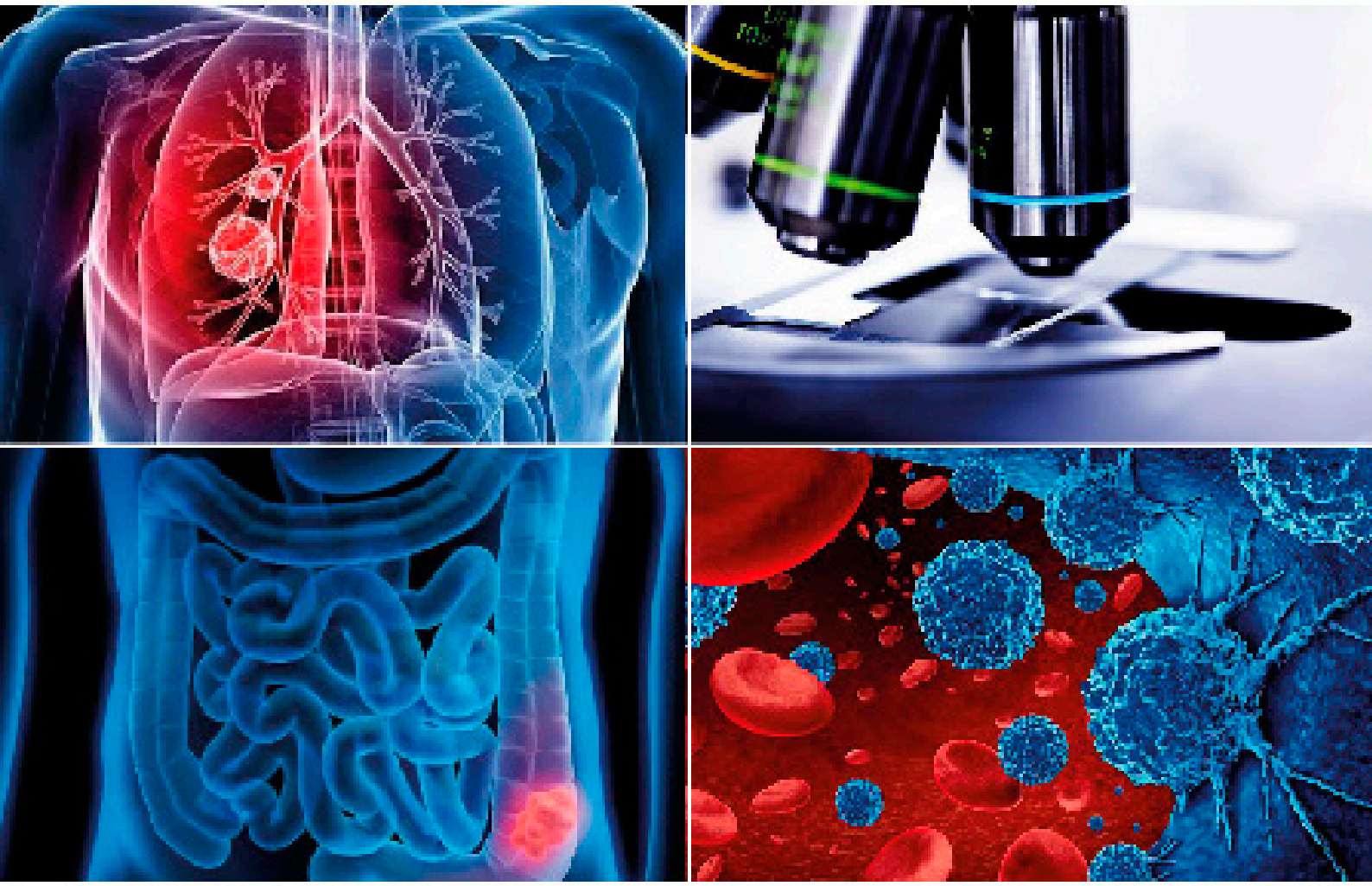

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EDITORIAL

Dear Colleagues,

The Republic of Turkey, which was established on October 29, 1923, rose on the wings of science and technology, raising generations who are curious, questioning, researching, free of mind, free of conscience, and free of wisdom. As the Journal of Current Hematology & Oncology Research (JCHOR) team, we, as the scientists of the country, have been trying to carry the values of our Republic even further since we started our publishing life. JCHOR aims to present its readers with articles on new and exciting topics in the field of hematology and oncology in each issue. In our three issues published in 2023, we published 8 research articles, 4 reviews, and 5 case report articles. On the 100th anniversary of our Republic, as the Journal of Current Hematology & Oncology Research team, we wish you many more centenaries full of research. As Mustafa Kemal Atatürk said, "The rising new generation; the future is yours. We founded the Republic, you are the ones to elevate it and keep it alive !".

Long live the Republic!

Prof. İlhami BERBER
Editor in Chief

Journal of Current
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Journal of Current Hematology & Oncology Research

Original Article

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The relationship between immunologic system and ferritin levels in patients with transfusion dependent thalassemia: a retrospective single-center study

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ABSTRACT

Aims: Thalassemia is an inherited anemia characterized by reduced or absent expression of α- or ß-globulin genes.[1] Transfusion dependent thalassemia (TDT) has an increased risk for serious infections, suggesting that a fundamental defect.

Methods: The study included 61 patients with TDT between the ages of 18 and 45 who were followed up in the hematology clinic of our tertiary care center between 2018 and 2023. For the determination of mononuclear cell surface markers, peripheral blood was processed according to standard procedures, labeled with monoclonal antibodies specific for CD4, CD8, CD3, CD19, and CD56, and analyzed by cytofluorometric analysis with a FACScan flow cytometer (Sysmex UF 1600).

Results: In our study, CD4, CD8, CD3, CD19, and CD56 values, which are lymphocyte markers, were examined to evaluate the immune system of patients diagnosed with TDT, and it was observed that there was no significant correlation between these values and the annual infection frequency and mean ferritin values of the patients.

Conclusion: The mean age of the 61 patients included in the study was 24.83±6.02 years, and 33 were female and 28 were male. The mean ferritin value was 3150.88±2553.51 ng/ml, and transferrin saturation was 42.42±14.43. The mean number of transfusions per year was 15.39±1.90, and the mean number of detectable infections per year was 2.85±2.02.

Keywords: Transfusion dependent thalassemia, immunologic system, ferritin

INTRODUCTION

Thalassemia is an inherited anemia characterized by reduced or absent expression of α- or β-globulin genes.[1] It is prevalent in the Mediterranean region as well as in the Far East and equatorial countries in the world, and approximately over 40.000 new patients are diagnosed each year. Due to the high frequency of consanguineous marriages, approximately 300 babies with thalassemia are born in our country every year, and this constitutes an important problem.[2] The prevalence of thalassemia carriage in Turkey is reported to be 2%, and this rate varies regionally (0.6%±13.1%).[3] Beta thalassemia occurs as a result of various mutations (quantitative defect in globin chain synthesis), primarily in the genes encoding globin chains on chromosome 11, may be transfusion dependent (TDT), and is an autosomal recessive disease.[4]

TDT has an increased risk for serious infections, suggesting that a fundamental defect in host defenses is present, which may be associated with iron overload, chronic immune stimulation by repeated blood transfusions, splenectomy, and immunodeficiency. The effects of iron overload include reduced antibody-mediated and mitogen-stimulated phagocytosis by monocytes and macrophages, changes in T-lymphocyte subsets, and modification of lymphocyte distribution in different parts of the immune system.[5] Infections are a common complication of thalassemia (12-13%) and can be fatal.[6] Infections are one of the top two causes of mortality in thalassemia, along with heart failure.[7] Some studies have demonstrated decreased activity of T and B lymphocytes, neutrophils, macrophages, and complement. Therefore, patients with β thalassemia major should be regularly screened for immune systems.

Although the relationship between thalassemia infection and thalassemia immunologic markers has been investigated many times, the number of studies investigating the relationship between increased iron load and immunologic status in transfusion-dependent thalassemia (TDT) patients is limited. In our study, we aimed to retrospectively investigate whether there is a relationship between these cells and ferritin levels in patients with β thalassemia major who were previously screened for T, B, and NK cell markers by flow cytometry in our center.

METHODS

The study included 61 patients with TDT between the ages of 18 and 45 who were followed up in the hematology clinic of our tertiary care center between 2018 and 2023. Patients with primary immunodeficiency and patients with chronic diseases that may lead to secondary immunodeficiency were excluded. Approval for the study was obtained from the Harran University Clinical Researches Ethics Committee with the decision number HRÜ/23.09.02 and date 22.05.2023. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patients were also evaluated according to whether they had a splenectomy or not, and it was seen that 34 of the patients had a splenectomy. The demographic data of the patients is presented in Table 1.

Table 1. Sociodemographic and clinical characteristics

Variables	n	%
Age		
Mean ± SD	24.83 ± 6.02	
Median (min-max)	23 (18-45)	
Gender		
Female	33	54.1
Male	28	45.9
Splenectomy		
No	27	44.3
Yes	34	55.7
Parameters	**Mean ± SD**	
Ferritin	3150.88 ± 2553.51	
Number of transfusions per year	15.39 ± 1.90	
Saturation of transfer	42.42 ± 14.43	
CD19 B	12.73 ± 5.52	
CD3 T LENF	73.39 ± 9.47	
CD3, CD4 TLENF	58.90 ± 10.78	
CD3, CD8 T LENF	38.72 ± 13.41	
CD4/CD8 T	1.63 ± 0.60	
CD3- CD56+ NK	10.62 ± 5.02	
CD3 HLADR+ T	12.31 ± 11.23	
Number of infections per year	2.85 ± 2.02	

Serum ferritin was measured by the ELISA method. The 12-month mean serum ferritin value and serum transfusion saturation were used to measure iron toxicity and accumulation in patients diagnosed with TDT.[8] For the follow-up of the infection status of the patients, the applications to the infectious diseases department and the patients diagnosed by this department were retrospectively screened, and one-year applications were evaluated.

Quantification of serum immunoglobulins was performed by the radial immunodiffusion technique (Behring turbometer). For the determination of mononuclear cell surface markers, peripheral blood was processed according to standard procedures, labeled with monoclonal antibodies specific for CD4, CD8, CD3, CD19, and CD56, and analyzed by cytofluorometric analysis with a FACScan flow cytometer (Sysmex UF 1600).

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as mean ± SD or median (IQR) for continuous variables. The data were analyzed for normal distribution by the Kolmogorov-Smirnov test, and since $p<0.05$, the Mann-Whitney U test, a nonparametric test, was used for pair-wise group comparisons with continuous variables. The relationship between continuous variables was analyzed by the Spearman correlation test. $p<0.05$ was considered statistically significant.

CONCLUSION

The mean age of the 61 patients included in the study was 24.83±6.02 years, and 33 were female and 28 were male. The mean ferritin value was 3150.88±2553.51 ng/ml, and transferrin saturation was 42.42±14.43. The mean number of transfusions per year was 15.39±1.90, and the mean number of detectable infections per year was 2.85±2.02. The sociodemographic and clinical characteristics of the patients are presented in Table 1.

CD3+ levels were measured in all patients, and the mean was 73.39±9.47%. No significant difference was found in CD3+ levels of splenectomized patients compared to non-splenectomized patients (p=0.36) (Table 2). There was also no significant difference between CD3+ levels and ferritin and transferrin saturation values. There was no significant difference between CD3+ levels and the number of infections per year. CD 3 HLADR+T cells were significantly higher in patients who underwent splenectomy (p=0.014) and CD 3 HLADR+T cells were increased in patients with frequent infections, but this was not statistically significant (p=0.144) (Table 3).

Table 2. Comparison of various clinical parameters with splenectomy

	Splenectomy		
Variables	**No N=27 Median (IQR)**	**Yes N=34 Median (IQR)**	**p**
CD19 B	12.0 (6.0)	12.0 (10.5)	0.721
CD3 T LENF	75.0 (11.0)	72.5 (11.5)	0.360
CD3,CD4 TLENF	60.0 (19.0)	57.0 (12.2)	0.760
CD3,CD8 T LENF	39.0 (21.0)	35.0 (12.7)	0.416
CD4/CD8 T	1.3 (1.1)	1.6 (0.8)	0.576
CD3- CD56+ NK	10.0 (8.0)	10.0 (6.5)	0.457
CD3 HLADR+ T	8.0 (8.0)	12.0 (10.5)	**0.014**

Mann whitney U test, p<0.05 statistically significant

Helper T cells were measured in all patients, and the mean value was 58.90±10.78%. There was no significant difference in CD4+ levels in splenectomized patients compared to non-splenectomized patients (p=0.76). There was also no significant difference between CD4+ levels and ferritin and transferrin saturation values (p=0.5 and p=0.49, respectively). There was also no significant difference between CD4+ levels and the number of infections seen in one year (p=0.8) (Table 3).

The mean cytotoxic T cell levels were 38.72±13.41% in all patients, and no significant difference was found between the splenectomy and non-splenectomy groups (p=0.41) (Table 2). In addition, no significant difference was found between CD8+

levels and ferritin (p=0.73), transferrin saturation (p=0.83) and the number of detectable annual infections (p=0.96).

The CD4/CD8/CD8 ell ratio was found to be in the normal range, with a mean of 1.63±0.60. This value was 1.3 in non-splenectomized patients and 1.6 in splenectomized patients, and no statistically significant difference was found (p=0.57). There was no significant difference in CD4/CD8 T cell ratio with ferritin (p=0.58), transferrin saturation (p=0.75) and the number of detectable infections per year (p=0.96).

CD56+ natural killer (NK) cells were evaluated in the study, and the mean value was 10.62±5.02%. CD56+ values were statistically similar in the splenectomized and non-splenectomized groups (p=0.45). In addition, NK cells did not change with ferritin value (p=0.34), transferrin saturation (p=0.25) and number of infections (p=0.91).

Finally, B lymphocyte marker CD19+ values were also evaluated in the study, and the mean value was 12.73±5.52 %. CD19+ values were statistically similar in the splenectomized and non-splenectomized groups (p=0.71). There was no significant difference between CD19+ value and ferritin (p=0.48), transferrin saturation (p=0.86), but CD19+ value increased as the annual number of detectable infections increased, but this increase was not statistically significant (p=0.2).

Table 3. Relationship between various clinical parameters

		Ferritin	Saturation of transfer	Number of infections per year
CD19 B	r	0.091	-0.022	0.165
	p	0.483	0.866	0.205
CD3 T LENF	r	-0.182	-0.040	-0.196
	p	0.161	0.758	0.130
CD3,CD4 TLENF	r	-0.087	-0.090	-0.033
	p	0.503	0.491	0.803
CD3,CD8 T LENF	r	-0.027	-0.045	-0.006
	p	0.834	0.730	0.965
CD4/CD8 T	r	-0.071	-0.040	-0.006
	p	0.588	0.757	0.961
CD3- CD56 + NK	r	-0.123	-0.147	0.015
	p	0.346	0.257	0.911
CD3 HLADR + T	r	0.016	-0.014	0.189
	p	0.901	0.914	0.144

Spearman correlation test

DISCUSSION

Infectious complications, which are associated with morbidity and mortality in patients with TDT, constitute an important part of the clinical spectrum of β-thalassemia.[9] In our study, CD4, CD8, CD3, CD19, and CD56 values, which are lymphocyte markers, were examined to evaluate the immune system of patients diagnosed with TDT, and it was observed that there was no significant correlation between these values and the annual infection frequency and mean ferritin values of the patients.

In the study by Ezer et al.[10] lymphocyte subgroups of 27 children diagnosed with thalassemia major were examined. In this study, 15 of 27 patients were splenectomized, and unlike our study, 12 patients diagnosed with the thalassemia trait were included in the study, and a control group was added to the study. Again, unlike our study, the CD8+ level was found to be significantly higher in the non-splenectomized group in this study. In addition, CD19+ levels were also found to be significantly higher in patients diagnosed with thalassemia in this study. In this study, there was no comparison between ferritin value and lymphocyte subgroups in children diagnosed with thalassemia.

In the study by Rakhmanova et al.[11], CD4, CD8, CD3, and CD16 levels as immune markers, IL-6 and IFN-β values, and ferritin values were examined in 200 patients aged between 1 and 27 years. It was not specified how many of the patients were in the adult age range. In this study, the CD3+ cell ratio was found to be high at 39.5%, but unlike our study, immune markers and lymphocyte subgroups were not compared with splenectomy and ferritin levels. However, the fact that CD3 HLADR+ T cells were found to be high, especially in patients with splenectomy, in our study may be considered a similarity between the two studies.

In the study conducted by Ehsanipour et al.[12] in 106 patients aged between 4 and 50 years, many parameters, including complement levels, lymphocyte markers, immunoglobulin levels, use of chelator drugs, ferritin, and age, were examined. Similar to our study, lymphocyte markers were also examined in patients, and similar to our study, no significant correlation was found between splenectomy, ferritin levels, and lymphocyte markers. Unlike our study, the adult age group was not evaluated separately in this study, and the relationship between the frequency of infection and lymphocyte sub-markers was not investigated.

The number of studies evaluating the relationship between the immune system and ferritin levels in patients with TBI in the adult age group is limited. In our study, we contributed to this deficiency in the literature. The biggest shortcoming of our study is that it was conducted at a single center. Studies involving a larger number of centers and patients are needed to confirm the relationship between ferritin, which is an indicator of iron load, and the immune system in patients with TBI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethical Committe of Faculty of Harran University (Date: 22.05.2023, Decision No: HRÜ/23.09.02).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Evaluation of the frequency of hepatitis B virus reactivation and the importance of hepatitis B prophylaxis in hematology patients receiving immunosuppressive therapy: a single-center study

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ABSTRACT

Aims: The aim of this study was to evaluate the rate of hepatitis B virus reactivation (HBVr) in hematology patients receiving immunosuppressive therapy in our center and the clinical characteristics of patients with HBVr. We will also investigate the importance of effective prevention of this potentially life-threatening event and management of hepatitis B virus (HBV) prophylaxis.

Methods: In this study, hepatitis B prophylaxis and its effects on patients over 18 years of age receiving immunosuppressive therapy in the hematology clinic were analyzed. 122 patients were included in the study. The HBV markers of the patients were determined by the chemiluminescence method. In the study, HbsAg(+) and isolated antiHbc IgG-positive patients received prophylactic antiviral treatment. The differential diagnosis of HBV reactivation and the criteria determined to define HBV reactivation were performed. Clinical characteristics and descriptive information of patients receiving HBV prophylaxis were analyzed using SPSS 25.0.

Results: The median age of 122 patients (59.8% male) was 58 years. It was determined that five HbsAg-positive patients had no prior follow-up and did not receive antiviral treatment. 117 patients had isolated anti-HBc IgG positivity. The median duration of prophylaxis was 15 (9-21.25) months, and the total follow-up period was 19.5 (11.75-30.25) months. 81.1% of the patients received regular HBV prophylaxis treatment; 59% of them received entecavir, and the rest received tenofovir disoproxil. Bone marrow transplantation was performed in 25 patients. HBV reactivation was detected in only 4 patients (3.3%); one of these patients had received allogeneic and one autologous bone marrow transplantation; and three patients had received chemoimmunotherapy including Rituximab. The diagnoses of the patients with HBVr were acute myeloid leukemia, lymphoma, and chronic lymphocytic leukemia. During the follow-up period, 29 patients (23.8%) died due to their primary disease, but there were no deaths due to HBV reactivation.

Conclusion: The data obtained in this study show that effective hepatitis B prophylaxis treatment is successful in preventing HBV reactivation in hematology patients. HBVr was observed in four patients who did not take HBV prophylaxis medication regularly.

Keywords: Hematology, immunosuppressive therapy, hepatitis B, prophylaxis, reactivation

INTRODUCTION

Hepatitis B carriage [HBsAg(+), Anti-HBs (-)] is a condition in which the patient has previously been exposed to the hepatitis B virus and has not developed immunity to it. Healed hepatitis B is a condition in which the patient has encountered hepatitis B at some point in his/her life and has developed immunity and antibodies [HBsAg(-), antiHc IgG(+)]. Over time, these antibodies decrease in the body, and when the patient is exposed to hepatitis B again

or uses immunosuppressive drugs such as chemotherapy, hepatitis B viremia occurs in the patient. Hepatitis B viremia leads to acute fulminant hepatitis, cirrhosis, and even hepatocellular cancer, resulting in fatal complications.[1,2] Cortisone, rituximab (anti-CD20), and other cytotoxic chemotherapy drugs, which are widely used in benign and malignant diseases of hematology, both reduce the number of cells involved in the immune system and weaken the immune system by dysfunctioning these cells, leading to hepatitis B virus reactivation (HBVr).[3] In addition, these life-saving chemotherapy treatments are interrupted when HBVr occurs. To prevent this situation, prophylactic antiviral treatment should be initiated to prevent HBVr in HbsAg positive carriers and in hematology patients who will receive immunosuppressive treatment such as chemotherapy and rituximab in isolated antiHbc IgG positive patients.[4] Hepatitis B prophylaxis is important in the treatment of these patients because HBVr has the potential to negatively affect clinical outcomes by reducing the chance of cure and preventing the completion of cancer treatment.[5] HBVr causes serious problems in branches such as hematology, oncology, dermatology, rheumatology, nephrology, and neurology receiving immunosuppressive therapy and hepatitis B virus screening before treatment is usually neglected. In this study, we aimed to raise awareness among clinicians by determining the reactivation rate and clinical characteristics of hematology patients receiving immunosuppressive therapy.

METHODS

The ethics committee approval of the study was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Research Ethics Committee on 22.05.2020 with the decision number 2020/03-50. The analyses in the study were performed according to the principles of the Declaration of Helsinki.

This study included patients aged ≥18 years who started immunosuppressive treatment and received hepatitis B prophylaxis in the hematology clinic between January 2016 and May 2020 at Van Yüzüncü Yıl University Medical Faculty Hospital. The information of the patients was retrospectively analyzed from the hospital's data processing system and patient files. Information on 134 patients was obtained in the study. A total of 12 patients were excluded from the study because 7 of these patients preferred another center for treatment in the following periods; 3 patients died in the first month of chemotherapy; and 2 patients did not have sufficient information in their file records. Thus, a total of 122 patients were included in the study. HbsAg, anti-Hbc IgG, anti-Hbs, anti-HIV, and anti-HCV status of patients receiving chemotherapy and immunosuppressive treatment such as rituximab were recorded from the patient records. These antiviral tests were performed by the chemiluminescence method (Abbott Diagnostics, ARCHITECT i1000 SR Immunoassay Analyzer, Germany). Age, gender, diagnoses, chemotherapies, number of cycles, number of transplanted patients, antiviral treatments, and duration were determined. Prophylactic antiviral treatment was initiated in patients with HbsAg(+) and isolated antiHbc IgG-positive patients. HBVr criteria were defined as transaminase elevation of at least five times or more, bilirubin increase, PT/INR increase, HBsAg or HBeAg reappearance, and HBV DNA increase. A differential diagnosis of HBV reactivation from sepsis, chemotherapy toxicity, and cholestasis was made. The number and clinical characteristics of patients with HBV reactivation were determined.

Statistical Analysis

SPSS version 25.0 (IBM SPSS, Chicago, IL) was used to calculate descriptive data on HBVr patient characteristics. Numerical data were presented as medians (Q25-Q75). Categorical variables were expressed as numbers and percentages (n, %).

RESULTS

A total of 122 patients, 73 (59.8%) of whom were male, were included in the study. The median age of the patients was 58 years. Five (4.1%) patients who were HbsAg positive had no previous clinical follow-up and were not receiving any antiviral treatment for HBV. Isolated anti-Hbc IgG positivity was detected in 117 patients in the study. The median duration of total prophylaxis was 15 months. 99 (81.1%) of the patients received antiviral prophylaxis treatment regularly. As antiviral treatment, 72 (59%) patients received entecavir, and the remaining patients received tenofovir disoproxil. Bone marrow transplantation was performed in 25 (20.5%) patients. The demographic and clinical characteristics of the patients are shown in Table I. The study population consisted of patients (n=114/ 93.4%), the majority of whom received chemotherapy for malignant diseases. The immunosuppressive treatments given to the patients consisted of cytotoxic chemotherapy, cytotoxic chemotherapy regimens with Rituximab, and Rituximab alone. Table II shows the hematologic diseases of the patients and the characteristics of the chemotherapy regimens they received. HBV reactivation occurred in only 4 (3.3%) of 122 patients. Two patients with HBV reactivation had undergone bone marrow transplantation, and both patients did not receive antiviral treatment regularly. Patients 3 and 4 with HBV reactivation were diagnosed with chronic lymphocytic leukemia and received Rituximab chemotherapy regimens. The clinical characteristics of patients with hepatitis B reactivation are shown in Table III. During follow-up, 29 (23.8%) patients died due to disease recurrence and complications. No patient died due to HBV reactivation.

DISCUSSION

Approximately 400 million people worldwide are chronically infected with HBV, which is defined as hepatitis B surface antigen (HBsAg) in serum.[1] Hepatitis B carriage [HbsAg (+), anti-HbsAg (-)] is observed at a rate of 2.6% in the Turkish population, and hepatitis B carriage in the Eastern and Southeastern regions is 3.2%.[6] In another study, while HBsAg positivity was found to be approximately 4% in Turkey, anti-HBc IgG positivity was found to be 30.6%.[7]

The risk of hepatitis B reactivation is present in hematology patients receiving chemotherapy or immunosuppressive therapy with chronic hepatitis B [HBsAg (+)] or cured infection (anti-HBc-positive).[5] The risk of HBVr in HBsAg (-), and anti-HBc IgG (+) individuals is 0.3-9%. Although reactivation is low in those with anti-HBs (+), the risk is present. The risk of reactivation in HBsAg (+) individuals ranges from 4-70% and is usually above 10%. In this study, two out of five HBsAg-positive patients (40%) had HBVr. The aim of hepatitis B prophylaxis is to prevent serious clinical

Table 1. Demographic and clinical characteristics of the patients

Clinical parameters	n (%) or median (Q1-Q3)
Age, years	58 (46.25-68)
Gender Male Female	 73 (59.8%) 49 (40.2%)
Disease group Malign Bening	 114 (93.4%) 8 (6.6%)
Serological status HbsAg(+)/antiHbc IgG(+) HbsAg(-)/antiHbc IgG(+)	 5 (4.1%) 117 (95.9%)
AntiHbs status AntiHbs(-) AntiHbs(+)	 89 (73%) 33 (27%)
Immunosuppressive treatment Cytotoxic CT Rituximab+ Cytotoxic CT Rituximab	 66 (54.1%) 48 (39.3%) 8 (6.6%)
Immunosuppressive exposure (months)	6 (5-8)
Duration of prophylaxis (months)	15 (9-21.25)
Total follow-up time (months)	19.5 (11.75-30.25)
Antiviral treatment Entecavir Tenofovir disoproxil	 72 (59%) 50 (41%)
Compliance with immunosuppressive therapy Received regularly Not taken regularly	 99 (81.1%) 23 (18.9%)
HSCT Transplanted Non-transplant	 25 (20.5%) 97 (79.5%)
Hepatitis B reactivation status Reactivated Non-reactivated	 4 (3.3%) 118 (96.7%)

CT, Chemotherapy; HSCT, Hematopoietic stem cell transplantation

Table 2. Hematologic diseases and chemoimmunotherapies

Primary disease	n (%)	Chemotherapies given
Multiple myeloma	26 (21.3%)	* VAD, VCD, VRD,
Chronic lymphocytic leukemia	21 (17.2%)	** R-FC, RB
NHL (DLBCL)	21 (17.2%)	** R-CHOP, R-DHAP, R-ICE
Acute myeloid leukemia	19 (15.6%)	*7+3, HIDAC, FLAG-IDA
Hodgkin's lymphoma	15 (12.3%)	*ABVD, DHAP, ICE
Acute lymphocytic leukemia	6 (4.9%)	*Hyper-CVAD(A/B), CALGB
NHL (Other)	6 (4.9%)	*CHOP, CHOEP, R-ESHAP
ITP	5 (4.1%)	Rituximab
TTP	2 (1.6%)	Rituximab
AIHA	1 (1.8%)	Rituximab

*Cytotoxic chemotherapy, **Rituximab + cytotoxic chemotherapy
NHL, non-hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; ITP, immune thrombocytopenic purpura; TTP, thrombocytopenic thrombotic purpura; AIHA, autoimmune hemolytic anemia

consequences of HBVr, such as acute-fulminant hepatitis and liver failure. Hepatitis B prophylaxis is necessary according to the indications and evidence provided by current international recommendations and to prevent interruption of life-saving anti-neoplastic therapies.[8] In this study, HBVr was observed in 4 (3.3%) patients, and only these patients had a morbidity burden. For prophylactic antiviral treatment to be effective, HBV prophylaxis should be started 2 weeks before immunosuppressive therapy or chemotherapy and continued for 12-18 months after the end of treatment.[4] In

Table 3. Characteristics of patients with hepatitis B reactivation

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	39	42	59	54
Gender	Female	Male	Male	Male
Malignant Disease	AML	DLBCL	CLL	CLL
Received CT	7+3, HIDAC, Busulfan+ Cyclophosphamide, Cyclosporin, FLAG-IDA	R-CHOP, R-DHAP, Busulfan+ Etoposide	R-FC, RB	R-FC, RB
Total number of CT cycles	6	8	9	10
Stem cell transplant	Yes, [1]ASCT	Yes, [2]ASCT	No	No
Initial hepatitis serology	HbsAg(-), antiHbs(-), antiHbc Ig G(+)	HbsAg(+), antiHbs(-), antiHbc Ig G(+)	HbsAg(-), antiHbs(-), antiHbc Ig G(+)	HbsAg(+), antiHbs(-), antiHbc Ig G(+)
Prophylaxis monitoring	Not taken regularly	Not taken regularly	Not taken regularly	Not taken regularly
How many months reactivated (month)	11	15	10	9
Total Duration of prophylaxis (months)	11	11	13	8
Total follow-up period (months)	16	28	26	18
Laboratory values when reactivated	ALT=522 U/L, AST=486 U/L, TB=9.85 mg/dl, INR=2.1	ALT=880 U/L, AST=821 U/L, TB=7.26 mg/dl, INR=1.9	ALT=670 U/L, AST=804 U/L, TB=5.02 mg/dl, INR=1.6	ALT=640 U/L, AST=530 U/L, TB=7.8 mg/dl, INR=2.3
HBV DNA monitoring	Reactivation onset: 82000 IU/mL	Reactivation onset: 214300 IU/mL	Reactivation onset: 104000 IU/mL	Reactivation onset: 326400 IU/mL
HBV treatment	Tenofovir	Tenofovir	Entecavir	Entecavir
The day chemotherapy is delayed	22 days after ASCT, (cyclosporine)	After OSCT, there was no delay	43	38
Latest status	Malignancy recurrence, Ex	Alive	Alive	R/R malignancy, Ex

CT, Chemotherapy; AML, Acute myeloid leukemia; DLBCL, Diffuse large B cell lymphoma; CLL, Chronic lymphocytic leukemia; TB, Total bilirubin; R/R, Relapse/Refractory; 1ASCT, Allogeneic stem cell transplantation; 2ASCT, Autologous stem cell transplantation

this study, HBV prophylaxis was started simultaneously with chemoimmunotherapy because the treatment of hematologic malignancies was urgent. HBVr was not observed in any of these patients because HBV prophylaxis was not started before chemotherapy. In our study, HBVr was observed in patients who did not use HBV prophylaxis regularly and discontinued it for a long time.

Apart from malignant hematologic diseases, HBV prophylaxis is also given to benign patients receiving immunosuppressive therapy. In a study by Xu et al.[9], the positivity of hepatitis B markers in 115 rheumatoid arthritis patients was evaluated, and all patients were given leflunomide, an immunosuppressive drug. In this study, HBVr was observed in five patients with chronic hepatitis B (HbsAg positive, antiHbc IgG positive, HBV DNA normal) who did not receive HBV prophylaxis. In our study, HBVR was not observed in patients receiving immunosuppressive treatment for benign disease because they received HBV

prophylaxis regularly. However, HBVr was observed in two patients with malignant hematologic disease who were HbsAg positive and did not receive HBV prophylaxis regularly.

Understanding the role of novel and specific antineoplastic agents such as the anti-CD 20 agent Rituximab in the generation of HBVr represents an important step forward in prevention strategies.[10] Rituximab is a biologic drug that suppresses the immune system by acting on B lymphocytes. In people at risk of hepatitis B reactivation, it may particularly trigger this condition.[11] Huai-Hsuan Huang et al.[12] conducted one of the largest studies in this field in 3702 adult non-Hodgkin lymphoma patients receiving rituximab-based chemoimmunotherapy. In this study, antiviral treatment was started for HBV prophylaxis in 711 patients. As a result of this study, the survival of patients who received HBV prophylaxis was significantly higher than that of patients who did not receive HBV prophylaxis. In our study, 39.3% of patients received chemoimmunotherapy including Rituximab, and 6.6% received Rituximab for benign disease. HBV prophylaxis was initiated in all of these patients. HBVr occurred in three patients who received Rituximab for malignant hematologic diseases. HBV prophylaxis includes antiviral drugs such as lamivudine, entecavir, and tenofovir disoproxil. In a study by Alessandro Loglio et al.[13] the efficacy of Lamivudine given for prophylaxis was evaluated in 85 non-Hodgkin lymphoma patients receiving Rituximab-based chemoimmunotherapy. In this study, patients were receiving lamivudine prophylaxis regularly. HBVr was observed in one patient, and ALT elevation was observed in five patients. In a study by Nikolaos Papadopoulosa et al.[14] data from 55 patients, the majority of whom had hematologic malignancy, were analyzed. HBVr was observed in one of 31 patients who received any of the antiviral drugs, including lamivudine, entecavir, and tenofovir disoproxil. However, HBVr was observed in all 24 patients who did not receive HBV prophylaxis. Patients in our study used nucleoside analogs such as entecavir and tenofovir disoproxil, which are more effective than lamivudine, and these drugs were not stopped due to any side effects. The data obtained from these studies, including our study, show that all antiviral drugs used in HBV prophylaxis are effective in preventing HBVr.

HBV-naive patients should be vaccinated against HBV before stem cell transplantation. Up to 54% reactivation has been reported in HBsAg-positive stem cell transplantation patients. Reverse seroconversion is common in cases with anti-HBc (+). In allogeneic stem cell transplant recipients, 7-15% of post-transplant liver disease is caused by viral hepatitis. In cases of suspicion, HBV DNA should be tested from both the blood and collected stem cells of the donor. Immunosuppression causes reactivation of HBV replication on circular closed covalent DNA (cccDNA) in hepatocytes.[15] Cyclosporine, tacrolimus, rituximab, anti-thymocyte globulin globulin, and mycophenolate mofetil are agents used to suppress the immune system after hematopoietic stem cell transplantation (HSCT). Since these drugs suppress the immune system, they increase the risk of HBVr in patients with HSCT.[16] A retrospective study investigated the incidence of HBVr in 413 patients with hematologic malignancy who underwent HSCT.[17] HBVr developed in all five patients with HSCT who were HBsAg-positive. HBVr was detected in 11 of 408 HBsAg-negative HSCT patients. These individuals had different serologic markers (anti-HBc and/or anti-HBs). In this study, all HBVr cases were controlled with lamivudine or entecavir administration. In our study, 25 (20.5%) patients underwent HSCT. HBVr developed in two patients, one of whom underwent ASCT and the other underwent OSCT. The patient who underwent ASCT was HbsAg negative and anti-Hbc IgG positive. The patient who underwent OSCT was HbsAg and anti-Hbc IgG positive. HBVr was controlled with tenofovir disoproxil in both cases. HBV prophylaxis was successful with entecavir and tenofovir disoproxil in other HSCT patients without HBVr.

Limitation: Since the number of patients with HBV reactivation was 4/122, it was not possible to statistically evaluate the factors affecting reactivation. At the beginning of the treatment of hematologic malignancy, HBV DNA was studied only in patients with HbsAg(+) and during the reactivation period of patients with HBV reactivation. However, HBV DNA was not regularly studied in patients with isolated antiHbc IgG positivity and in the follow-up of patients with HBV reactivation. A liver biopsy was not performed in any patient with HBVr.

CONCLUSION

Before starting treatment for hematologic malignancies, especially viral hepatitis, markers should be checked. Hepatitis B prophylaxis should be given to malignant and benign hematology patients with anti-HBc IgG positivity who will receive rituximab, cytotoxic chemotherapy, stem cell transplantation, and other immunosuppressive therapies. The risk of viral hepatitis transmission is particularly high in malignant hematology patients since blood and blood products are frequently given during treatment and follow-up. Therefore, viral hepatitis markers should be reassessed at the start of chemoimmunotherapy even if HBV prophylaxis is not needed. HBV DNA should be studied before starting prophylaxis treatment if the hospital has the facility. In this study, HBVr was not found in any patient who received antiviral prophylaxis regularly during and after chemotherapy. In our study, HBVr was seen in patients with malignant hematologic diseases such as leukemia and lymphoma who did not receive prophylaxis regularly. In addition, these patients received rituximab-based chemoimmunotherapy in addition to stem cell transplantation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethics committee approval of the study was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 22.05.2020, Decision No: 2020/03-50).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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The place of initial serum sodium and globulin ratio in the prognosis estimation of patients with lung cancer

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ABSTRACT

Aims: Since lung cancer is a disease with a high mortality and morbidity rate, determining its prognosis has a very important place. Studies in the literature have shown that electrolyte disturbance and inflammation may be associated with a poor prognosis in lung cancer, however, further studies are needed on this subject. In this study, it was planned to investigate the role of the sodium and globulin ratio measured at the time of diagnosis in the prognosis prediction of patients with lung cancer diagnosis.

Methods: The study was carried out retrospectively from the patient files and hospital records of 165 patients who were followed up with the diagnosis of lung cancer between January 1, 2015 and January 1, 2021 in Kırıkkale University (KKU) Faculty of Medicine, Department of Internal Medicine, and Medical Oncology Department. Patients with achievable sodium, albumin, and total protein values at the time of diagnosis were included in the study. The hemogram parameters of the patients included in the study were creatinine and estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT) level, albumin level, total protein level and globulin level, C-reactive protein (CRP) level, CEA, and TSH levels. In addition, the sodium/globulin ratio (SGR) and the CRP/albumin ratio (CAR) were evaluated.

Results: 87.3% of the patients were male, and 12.7% were female. The mean age at presentation was 62.5±9.1 years. Adenocancer accounts for 46.1% of cancers with 76 patients, squamous cell carcinoma for 41.8% with 69 patients, and small cell carcinoma for 12.1% with 20 patients. 11 (6.7%) of the patients were stage 1, 25 (15.2%) stage 2, 58 (35.2%) stage 3, and 71 (43%) stage 4 patients. 111 (67.3%) of the patients died. The average follow-up time is 16.6 months. In the regression analyzes performed in our study, mortality and sodium/globulin ratio (SGR) and progression-free survival and sodium/globulin ratio (SGR) were found to be unrelated. There was a weak negative correlation between the sodium/globulin ratio (SGR) and the CRP/albumin ratio (CAR). In the multivariate regression analysis, the stage of the disease, diabetes, and CRP level were found to be the independent variables affecting mortality and the stage of the disease affecting progression-free survival. ($p<0.001$).

Conclusion: Independent prognostic factors in patients with lung cancer; stage of disease for mortality, diabetes, and CRP level were found to be stages for progression-free survival. Considering the weak relationship between sodium/globulin ratio (SGR) and CRP/albumin ratio (CAR), SGR can be used as a future biomarker to predict prognosis in cancer patients. Further studies are needed to learn more about the relationship between SGR and lung cancer.

Keywords: Lung cancer, sodium, globulin, overall survival, mortality

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the world.[1] It is one of the diseases with high mortality and morbidity rates worldwide due to the increase in smoking rates in the population. The average life expectancy for lung cancer is 1 year, and the 5-year survival rate has been reported to be 19%. Therefore, lung cancer constitutes one of the biggest health problems in the world.[2]

Inflammation and the tumor microenvironment are factors in the development and progression of cancer.[3] Cells involved in the mechanism of inflammation may be influential factors in cancer formation, tumor progression, and patient survival.[3,4] Inflammation is often associated with the development and progression of cancer. Therefore, targeting the suppression of inflammation represents an important strategy for both cancer prevention and cancer treatment.[5] Clinical and epidemiologic studies suggest a strong association between chronic infection, inflammation, and lung cancer. Moreover, cancer-related

inflammation affects many aspects of malignancy, including the proliferation of malignant cells, angiogenesis, tumor metastasis, and response to chemotherapeutic drugs and hormones.[6]

Electrolyte disturbance is a common symptom in tumor patients, and previous research has found that this condition is associated with poor clinical outcomes in patients.[7] Hyponatremia is commonly seen in cancer patients and is associated with increased mortality and morbidity. Understanding the correct diagnosis and treatment of cancer-associated hyponatremia is critical to achieving better outcomes.[8]

An increased serum albumin and albumin/globulin ratio (AGR) has been reported to be associated with a favorable prognosis for various types of cancer.[9] A low albumin/globulin ratio (AGR) before treatment is associated with poor prognosis in cancer, and AGR can be used as a prognostic marker during cancer treatment.[10]

In China, a retrospective study was conducted in patients with gastric cancer, considering that the pretreatment sodium/globulin (SGO) ratio may be more meaningful in reflecting prognosis than sodium and globulin alone. SGO was found to predict sensitivity to chemotherapy more effectively than sodium or globulin alone and to be an independent and reliable prognostic factor.[11]

In our study, we planned to investigate the role of sodium and globulin levels and ratios at the time of diagnosis in the prognosis prediction of patients diagnosed with lung cancer. It was aimed at determining whether the sodium and globulin ratio at the time of diagnosis was related to the stage, comorbidities, and chemotherapy regimen of the patient diagnosed with lung cancer at the time of diagnosis and to find a cut-off value that could predict the prognosis.

METHODS

Study Design

The study was conducted retrospectively from the patient files and hospital records of patients who were followed up with a diagnosis of lung cancer between January 1, 2015 and January 1, 2021 in Kırıkkale University (KKU) Medical Faculty Hospital, Department of Internal Medicine, and Division of Medical Oncology. The study was initiated with the approval of the medical board, with decision number 2021.06.18. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participant Selection

Patients who were histopathologically diagnosed with lung cancer in the Department of Medical Oncology, who had evidence of primary tumor and/or metastasis by imaging, who had accessible sodium and globulin levels within the first three months of diagnosis, who were over 18 years of age, and who were followed for at least six months were included in the study. All patients received at least one course of chemotherapy. Patients with conditions that may affect serum sodium and plasma protein levels, such as stage 3 or more chronic kidney disease (CKD), cirrhosis, liver failure, advanced heart failure, central nervous system (CNS) diseases, hypothyroidism, malnutrition, the presence of an active infection, chronic inflammatory bowel disease, nephrotic syndrome, adrenal insufficiency, sepsis, diuretic use, and patients under 18 years of age, were excluded.

Parameters to be Examined

Patient characteristics (age, gender, smoking status, comorbidities, drug use), diagnostic characteristics (date of initial diagnosis, histopathologic subtype, stage, type, and duration of treatment), current health status (presence and date of mortality, presence and date of recurrence), Biochemical parameters (hemoglobin, platelet, leukocyte, C-reactive protein, urea, creatinine, alanine amino transferase, sodium, potassium, glomerular filtration rate, total protein, albumin, globulin, thyroid stimulating hormone, and carcinoembryonic antigen) were evaluated. To evaluate the chemotherapy response of the patients, response evaluation criteria in solid tumors (RECIST 1.1) records kept by the Department of Medical Oncology, Kırıkkale University Medical Faculty Hospital were scanned.

Study Procedure

Patients will be divided into two groups according to their current survival, as follows: (1) deceased; (2) survivors. Patient, diagnostic, and biochemical parameters will be compared between these two groups. Among the parameters analyzed, the relationship between recurrence and mortality, which are associated with prognosis, and serum sodium and globulin levels and sodium/globulin ratios at diagnosis, will be evaluated. In addition, the relationship between CRP/albumin ratio (CAO) and sodium/globulin ratio (SGO) will be evaluated.

Statistical Analysis

The IBM SPSS (Statistical Package for Social Sciences) version 25 program was used. The data were evaluated by the Shapiro-Wilk test and histogram to determine a normal distribution. Numerical variables were presented as mean ± SD or median (min-max), and nominal variables were presented as numbers (percentage) according to their distributional characteristics. In the evaluation of continuous numerical variables between two independent groups, the independent samples t-test was used in the presence of a normal distribution, and the Mann-Whitney U test was used in the absence of a normal distribution. Pearson's chi-square or Fisher's exact test was used for the comparison of categorical variables. Kaplan-Meier test and Cox-regression analysis were used for survival analysis and risk analysis, and the Spearman correlation test was used for correlation analysis. $p<0.05$ was considered significant.

RESULTS

A total of 392 files of 392 patients diagnosed with lung cancer admitted to Kırıkkale University Faculty of Medicine, Department of Oncology, between January 2015 and January 2021 were analyzed. The study data were obtained by a detailed examination of 165 files (144 male and 21 female) selected after excluding patients who did not meet the study criteria. The demographic characteristics of all patients included in the study are shown in Table 1. The mean age of the patients was 62.5±9.1 (mean±SD) years, the median follow-up period was 16.6 (5.3-76.2) months, and 111 patients died during the follow-up period (Table 1).

Table 1. Demographic characteristics of patients with lung cancer at diagnosis (n=165)

Age (Year)	62.5 ± 9.1
Gender n (%) Male Female	 144 (87.3) 21 (12.7)
Histopathology n (%) Adenocarcinoma Squamous cell carcinoma Small cell carcinoma	 76 (46.1) 69 (41.8) 20 (12.1)
Stage n (%) Stage 1 Stage 2 Stage 3 Stage 4	 11 (6.7) 25 (15.2) 58 (35.1) 71 (43)
Survival n (%) Alive Deceased	 54 (32.7) 111 (67.3)
Smoking n (%) Present None	 138 (83.6) 27 (16.4)
Diabetes n(%) Present None	 22 (13.3) 143 (86.7)
Hypertension n (%) Present None	 30 (18.2) 135 (81.8)
Coronary artery disease n (%) Present None	 11 (6.6) 154 (93.4)
Progression n (%) Present None	 123 (74.5) 42 (25.5)
Operation n (%) Present None	 46 (27.8) 119 (72.2)
Follow-up period (month)	16.6 (5.3-76.2)

Data are given as n (%), mean ± standard deviation or median (minimum-maximum).

The laboratory values of the patients with lung cancer included in the study at the time of diagnosis are given in Table 8. Albumin 4.2 mg/dl (2.3-5.1), globulin 2. mg/dl (1.8-4.6) and sodium 140 mEq/L (123-147) levels were within normal limits (Table 2).

Table 2. Laboratory values of patients with lung cancer at the time of diagnosis

Hemoglobin (g/dl)	13.7 (9.5-16.9)
Leukocytes (x 10^3/mm^3)	8.5 (2.4-23.3)
Platelet (x 10^3/mm^3)	273 (111-670)
C-reactive protein (mg/l)	12 (1-43)
Alanine aminotransferase (U/L)	15 (6-150)
Glomerular filtration rate (ml/min/1.73 m^2)	97.2±23.5
Total protein (mg/dl)	7.1±0.6
Albumin (mg/dl)	4.2 (2.3-5.1)
Globulin (mg/dl)	2.9 (1.8-4.6)
Urea (mg/dl)	32 (15-86)
Creatinine (mg/dl)	0.81 (0.4-1.9)
Sodium (mEq/L)	140 (123-147)
Potassium (mEq/L)	4.6±0.4
Sodium/Globulin	48 (27.2-77.7)
Thyroid stimulating hormone (u/U/ml)	1.2 (0.2-4.1)
Carcinoembryonic antigen (ng/ml)	4 (0.7-231)

Data are given as mean ± standard deviation or median (minimum-maximum).

Comparisons of demographic characteristics and laboratory values of surviving and deceased patients are shown in Tables 3 and 4.

Table 3. Demographic characteristics of lung cancer patients at diagnosis according to survival

	Mortality n=111	Survival n=54	p
Age (Year)	63.1 ± 9.6	61.3 ± 7.9	0.237
Male/Female n (%)	98/13 (88.3 /11.7)	46/8 (85.2 /14.8)	0.622
Stage n (%) Stage 1 Stage 2 Stage 3 Stage 4	 1 (9) 13 (11.7) 39 (35.1) 58 (52.3)	 10 (18.5) 12 (22.2) 19 (35.2) 13 (24.1)	**<0.001**
Smoking n (%) Present None	 94 (84.7) 17 (15.3)	 44 (81.5) 10 (18.5)	0.656
Diabetes n (%) Present None	 7 (6.3) 104 (93.7)	 15 (27.8) 39 (72.2)	**<0.001**
Hypertension n (%) Present None	 16 (14.4) 95 (85.6)	 14 (25.9) 40 (74.1)	0.08
Coronary artery disease n (%) Present None	 5 (4.5) 106 (95.5)	 6 (11.1) 48 (88.9)	0.206
Operation (%) Present None	 21 (18.9) 90 (81.1)	 25 (46.3) 29 (53.7)	**<0.001**

Data are presented as n (%), mean ± standard deviation, or median (minimum-maximum). p: Significance level of the difference between living and deceased patients

Table 4. Laboratory values at diagnosis according to survival in patients with lung cancer

	Mortality n=111	Survival n=54	p
Hemoglobin (g/dl)	13.6 (9.5-16.5)	13.7 (10-16.9)	0.48
Leukocytes (x 10^3/mm^3)	8.5 (2.7-23.3)	8.5 (2.4-22.7)	0.503
Platelet (x 10^3 /mm^3)	272 (111-670)	276 (136-600)	0.825
C-reactive protein (mg/L)	15 (1-43)	7 (1-37)	**0.001**
Alanine aminotransferase (U/L)	14 (6-150)	18 (7-103)	**0.049**
Glomerular filtration rate (ml/min/1.73 m^2)	99.8±24.9	93.2±19.9	0.09
Total protein (mg/dl)	7±0.6	7.2±0.5	0.06
Albumin (mg/dl)	4 (2.3-5)	4.3 (2.8-5.1)	**0.001**
Globulin (mg/dl)	3 (1.8-4.6)	2.8 (1.9-3.9)	0.495
Urea (mg/dl)	33 (17-86)	31 (15-80)	0.347
Creatinine (mg/dl)	0.8 (0.4-1.9)	0.9 (0.5-1.6)	0.133
Sodium (mEq/L)	139 (123-147)	140 (133-145)	0.640
Potassium (mEq/L)	4.6±0.5	4.5±0.3	0.234
Thyroid stimulating hormone (u/U/ml)	1.2 (0.2-4.3)	1.1 (0.3-4.1)	0.871
Carcinoembryonic antigen (ng/ml)	4.5 (0.7-183)	3.1 (0.8-231)	**0.001**
Sodium/globulin	47 (27.3-77.7)	49.3 (35.8-76.2)	0.477
C-reactive protein/Albumin	3.9 (0.2-12.9)	1.6 (0.22-10.1)	**<0.001**

Data are presented as n (%), mean ± standard deviation, or median (minimum-maximum). p: Significance level of the difference between living and deceased patients

There was a weak negative correlation between CRP and albumin ratio (CAO) and sodium, and a weak negative correlation between sodium/globulin ratio (SGO) and CAO (r=-0.278, p<0.001; r=-0.415, p<0.001; Figure 1 and Figure 2, respectively).

The Kaplan-Meier curve of cumulative survival for all lung cancer patients during follow-up is shown in Figure 3.

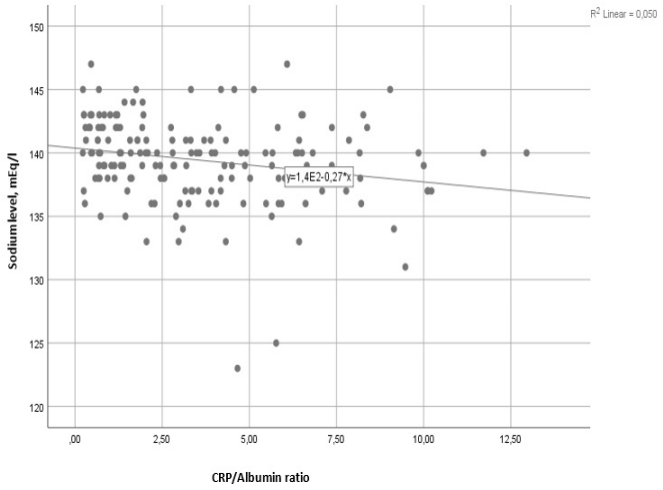

Figure 1. The relationship between serum sodium level and CRP/albumin ratio at diagnosis in patients with lung cancer (r=-0.278 and p<0.001 value)

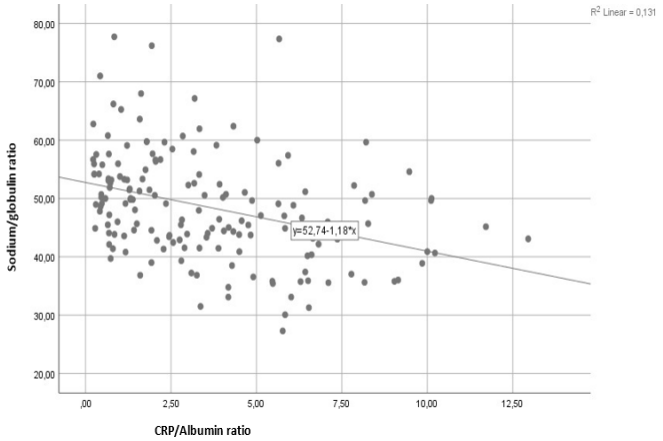

Figure 2. The relationship between serum sodium/globulin ratio and CRP/albumin ratio at diagnosis in patients with lung cancer (r= -0.415 and p<0.001)

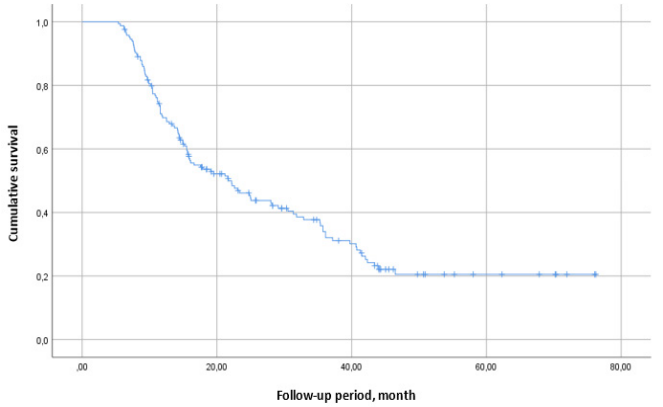

Figure 3. Kaplan-Meier curve of cumulative survival of all lung cancer patients during follow-up

The Kaplan-Meier curve of the cumulative survival of patients with lung cancer during follow-up according to their stage is given in Figure 4. Accordingly, there was a significant difference in survival between the four stages (log rank test p< 0.001).

The laboratory values of the patients with lung cancer included in the study at the time of diagnosis according to progression during follow-up are shown in Tables 5 and 6. Serum sodium, globulin, and sodium/globulin ratio at diagnosis were not significantly different between the two groups (p>0.05).

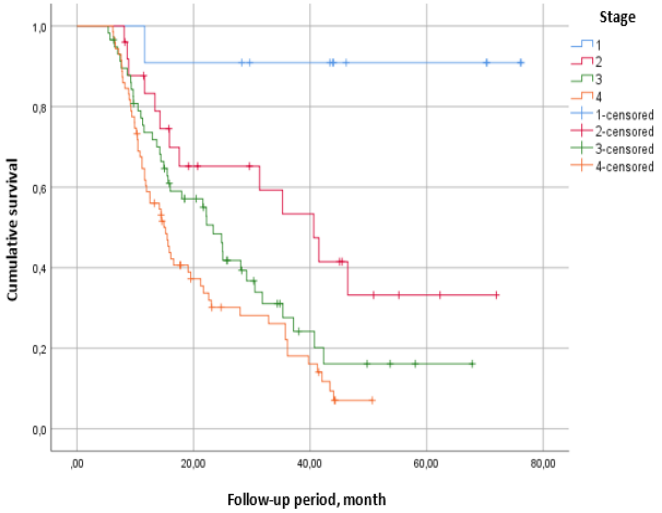

Figure 4. Kaplan-Meier curve of cumulative survival of patients with lung cancer according to stage (log rank test p<0.001)

The CEA value at diagnosis was significantly higher, and the total protein value was lower in patients with progression than those without progression (p<0.05). On the other hand, diabetes mellitus was more common in patients without progression compared to patients with progression, which was statistically significant. The presence of surgery was statistically significant in patients without progression compared to patients with progression. Progression was significantly higher (52.8%) in patients with stage 4 at the time of diagnosis compared to other stages (p<0.001). While the least progression was seen in stage 1 patients (1.6%), patients who did not show progression were mostly stage 3 patients (40.5%) (Table 5, 6).

Table 5. Demographic characteristics of lung cancer patients at diagnosis according to progression status

	Progression n:123	Non-progression n:42	p
Age (Year)	62.7 ± 9.2	61.9 ± 8.4	0.608
Male/Female n (%)	109/14 (88.6 /11.4)	35/7 (83.3 /16.7)	0.423
Stage n (%) Stage 1 Stage 2 Stage 3 Stage 4	 2 (1.6) 15 (12.2) 41 (33.3) 65 (52.8)	 9 (21.4) 10 (23.8) 17 (40.5) 6 (14.3)	**<0.001**
Smoking n (%) Present None	 103 (83.7) 20 (16.3)	 35 (83.3) 7 (16.7)	0.951
Diabetes n (%) Present None	 10 (8.1) 113 (91.9)	 12 (28.6) 30 (71.4)	**0.003**
Hypertension n (%) Present None	 18 (14.6) 105 (85.4)	 12 (28.6) 30 (71.4)	0.06
Coronary artery disease n (%) Present None	 7 (5.7) 116 (94.3)	 4 (9.5) 38 (90.5)	0.474
Operation n (%) Present None	 19 (15.4) 104 (84.6)	 27 (64.3) 15 (35.7)	**<0.001**

Data are given as n (%), mean ± standard deviation or median (minimum-maximum).
p: Significance level of the difference between patients with and without progression

Table 6. Laboratory values at diagnosis according to progression status of patients with lung cancer

	Progression n:123	Non-progression n:42	p
Hemoglobin (g/dl)	13.7 (9.5-16.5)	13.7 (10-16.9)	0.789
Leukocytes (x 10^3/mm^3)	8.38 (2.38-17.6)	8.88 (4.6-23.3)	0.324
Platelet (x 10^3/mm^3)	266 (111-670)	278 (136-600)	0.725
C-reactive protein (mg/L)	13 (1-43)	8.5 (2-37)	0.154
Alanine aminotransferase (U/L)	14 (6-150)	17 (7-103)	0.095
Glomerular filtration rate (ml/min/1.73 m^2)	99.3±23.2	92.8±24	0.130
Total protein (mg/dl)	7±0.5	7.2±0.4	**0.04**
Albumin (mg/dl)	4.16 (2.25-5)	4.17 (3.28-5)	0.497
Globulin (mg/dl)	2.9 (1.8-4.6)	3 (2.3-4.5)	0.284
Urea (mg/dl)	33 (17-86)	32 (15-80)	0.402
Serum creatinine (mg/dl)	0.81 (0.44-1.36)	0.83 (0.58-1.89)	0.476
Sodium (mEq/L)	140 (123-147)	140 (133-145)	0.750
Potassium (mEq/L)	4.6±0.4	4.5±0.3	0.694
Thyroid stimulating hormone (u/U/ml)	1.2 (0.2-4.3)	1.1 (0.3-4.1)	0.551
Carcinoembryonic antigen (ng/ml)	4.2 (0.7-231)	3.3 (0.8-103)	**0.019**
Sodium/globulin	48.9 (27.2-77.7)	46.5 (31.2-60.7)	0.281
C-reactive protein/albumin	3.3 (0.2-12.9)	1.9 (0.4-10.1)	0.137

Data are given as n (%), mean ± standard deviation or median (minimum-maximum).
p: Significance level of the difference between living and deceased patients

The Kaplan-Meier curve of the comparison of progression-free survival of all patients by stage is given in Figure 6. Accordingly, there was a significant difference in progression-free survival between the four stages (log rank test p<0.001).

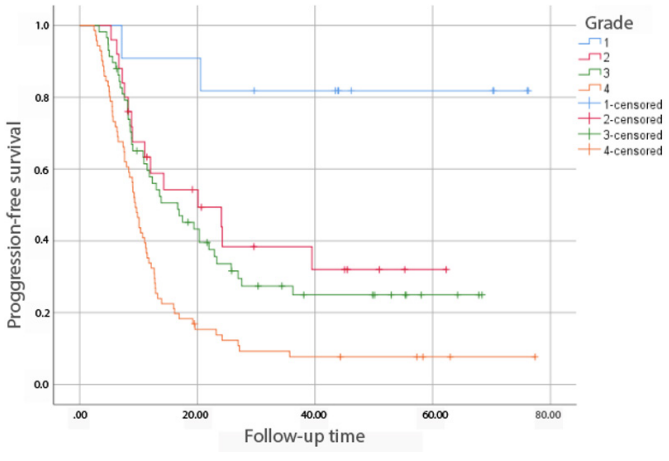

Figure 5. Kaplan-Meier curve of progression-free survival of all lung cancer patients by stage (log rank test p<0.001)

When the factors associated with mortality were analyzed by univariate Cox regression analysis, stage of the disease at diagnosis, presence of surgery, history of diabetes, albumin level, and CRP level were found to be significantly associated with mortality.

In multivariate Cox regression analysis, stage of the disease, patient's diagnosis of diabetes, and CRP level were determined as independent variables in predicting the mortality of patients with lung cancer. In multivariate Cox regression analysis, only the stage of the disease was determined as an independent variable in predicting progression-free survival.

Table 7. Factors affecting mortality in patients with lung cancer (univariate Cox regression analysis, n:165)

	Hazard rate (95% confidence range lower and upper limits)	p
Stage Stage 2-1 Stage 3-2 Stage 4-3	 9.08 (1.18-69.5) 16.36 (2.23-119.69) 23.2 (3.19-168.44)	 **0.034** **0.006** **0.002**
Albumin (mg/dl)	0.618 (0.430-0.889)	**0.009**
Carcinoembryonic antigen (ng/mL)	1.001 (0.996-1.006)	**0.608**
Total protein (mg/dl)	0.82 (0.57-1.16)	**0.265**
Alanine aminotransfer (U/L)	1.005 (0.993-1.019)	**0.409**
Glomerular filtration rate (ml/min/1.73 m^2)	1.005 (0.996-1.014)	**0.256**
C-reactive protein (mg/l)	1.027 (1.010-1.044)	**0.03**
Diabetes mellitus	0.33 (0.15-0.72)	**0.005**
Hypertension	0.67 (0.39-1.15)	**0.15**
Operation presence	0.34 (0.21-0.56)	**<0.001**

Data are given as median (minimum-maximum).
p: Significance level of the factors affecting mortality in univariate Cox regression analysis

In multivariate Cox regression analysis, stage of the disease, patient's diagnosis of diabetes, and CRP level were determined as independent variables in predicting the mortality of patients with lung cancer. In multivariate Cox regression analysis, only the stage of the disease was determined as an independent variable in predicting progression-free survival.

DISCUSSION

In our single-center study, we investigated whether serum sodium, globulin, and sodium/globulin levels at the time of diagnosis play a role in determining survival and progression-free survival in patients diagnosed with lung cancer over a five-year period. In this study, none of the serum sodium and globulin levels or sodium/globulin ratios at the time of diagnosis were found to be effective factors in predicting progression-free survival and mortality in patients diagnosed with lung cancer. The stage of the disease at diagnosis, diabetes, and CRP level were the determinants of mortality. The only factor affecting progression-free survival was the stage of the disease.

Electrolyte disturbance and systemic inflammation are two important causes of poor prognosis in cancer patients. Serum sodium and globulin levels are indicators of electrolyte homeostasis and inflammatory status. These markers have prognostic potential for cancer patients.[11] Patients with cancer often exhibit acid-base and electrolyte disturbances that complicate their treatment and prolong their hospitalization. These abnormalities have multifactorial mechanisms. Both the underlying disease and therapeutic interventions can contribute to their development.[9] Inflammatory cells and the chemokines and cytokines they produce affect tumor tissue by regulating the growth, migration, and differentiation of all cell types in the tumor microenvironment, including neoplastic cells, fibroblasts, and endothelial cells. Later in the tumorigenic process, neoplastic cells also direct inflammatory mechanisms such as selectin-ligand interactions, matrix metalloproteinase (MMP) production, and chemokine functions in favor of neoplastic invasion and metastasis. This may be part of the tumor's attempt to subvert immune cell functions. This sets the stage for tumor development.[12]

In cancer patients, hyponatremia is caused by malignancies, most commonly the syndrome of inappropriate antidiuretic hormone (SIADH) due to SCLC. Hyponatremia can also be triggered by the side effects of anticancer and palliative drugs.[13] The incidence of pretreatment hyponatremia has been found to be high in NSCLC patients as well as in SCLC patients. Hyponatremia is an independent prognostic factor for poor overall survival in lung cancer patients, especially in patients with NSCLC. Hyponatremia appears to be an independent predictor of lower survival in lung cancer patients, especially in patients with NSCLC.[14] These studies have demonstrated the relationship between changes in serum sodium levels during follow-up, mortality, and progression-free survival. In our study, we investigated whether there was a relationship between serum sodium levels at the time of diagnosis and mortality and between sodium levels and progression-free survival in patients diagnosed with lung cancer, and no significant relationship was found.

Abnormal serum albumin has been reported to be closely associated with the progression of many diseases. Moreover, previous studies have shown that decreased albumin levels are associated with an unfavorable prognosis for gastrointestinal cancers, including gastric, colorectal, and pancreatic cancers. In addition, serum globulin has been shown to have a close relationship with immunity and inflammation and to serve as a predictive value in tumor progression.[15] Serum globulin levels are known to be associated with chronic inflammatory diseases. In addition, an excess of inflammatory cells around the tumor has been found to be an accelerator parameter for tumor formation and proliferation.[16] In different studies, elevated globulin levels have been found to have serious adverse effects on cancer patients. Globulin levels have been reported to be associated with prognosis and survival in lung and gastric cancers.[17,18] Albumin and globulin are the main serum proteins and representative indicators of systemic inflammation. The albumin/globulin ratio is mainly used as a clinical indicator of multiple myeloma and other immunoproliferative disorders. Recently, the albumin/globulin ratio has been identified as a predictive value for long-term mortality in patients with nasopharyngeal carcinoma, colorectal cancer, lung cancer, and breast cancer.[19] In our study, serum albumin level at the time of diagnosis appeared to be a predictor of mortality in univariate regression analysis in patients diagnosed with lung cancer but had no effect on mortality in multiple regression analysis. Similarly, serum globulin level at the time of diagnosis were not a determinant of mortality. None of the serum total protein, albumin, or globulin levels at diagnosis were associated with progression-free survival.

The patient population diagnosed with lung cancer mostly consists of patients diagnosed with advanced stages. There are studies supporting this in the literature. Most of the patients' complaints and symptoms are non-specific. Therefore, the majority of patients are diagnosed at an advanced stage. Another 10% of patients are diagnosed incidentally with thoracic imaging without symptoms.[20,21] In our study, the majority of the patient population consisted of advanced-stage patients. A statistically significant correlation was found between the progressive stage of the disease and mortality. In addition, the risk of progression increased significantly as the stage progressed.

Lu et al.[22] examined pre- and postoperative CRP levels in patients diagnosed with gastric cancer and found that high CRP levels were associated with a poor prognosis. This may be related to angiogenesis in proinflammation, resulting in the proliferation of cancer cells and suppression of the immune response. In our study, there was a significant positive correlation between CRP level at the time of diagnosis and mortality in patients diagnosed with lung cancer. This result supports other studies in the literature.

Another parameter that has been widely studied as an inflammatory marker is the CRP/albumin ratio. In a study conducted by Tamagawa et al.[23], the preoperative CRP/albumin ratio was found to be a strong prognostic marker in patients with esophageal cancer. Vujic et al.[24] also showed that the CRP/albumin ratio is a useful prognostic factor in predicting overall survival in patients undergoing pancreatic surgery. In a study by Miyamoto et al.[25] investigating the role of CRP/albumin ratio in predicting short-term survival in patients with and without cancer diagnosis, the CRP/albumin ratio was shown to be a useful and independent factor in predicting short-term survival within two weeks. The possible reason for this is the increase in inflammation in cancer patients, the negative acute phase reactant of albumin, and its decrease due to malnutrition. In our study, a significant difference was found between the CRP/albumin ratio of surviving and deceased patients, and a significant inverse relationship was observed between the CRP/albumin ratio and survival. On the other hand, no significant relationship was found between the CRP/albumin ratio and progression-free survival.

In a study conducted by Zhang et al.[11] on patients with advanced gastric cancer, it was reported that the serum sodium/globulin ratio is an easily applicable marker that can effectively predict sensitivity to chemotherapy before first-line chemotherapy and may also be an independent and reliable prognostic factor to determine progression-free survival and overall survival in patients with advanced gastric cancer. In our study, no statistically significant difference was observed between the serum sodium/globulin ratios of survivors and deceased patients at the time of diagnosis. In addition, no significant correlation was found between progression-free survival and the sodium/globulin ratio.

In our study, only sodium and globulin were analyzed among the values that contribute to electrolyte disturbance and systemic inflammation. Therefore, it is not clear whether SGO is a good prognostic factor. Since our study population consisted of a few patients and was a retrospective study, longer follow-up periods and detection indices will be needed in the future to support these results. However, in our study, there was a weak negative correlation between CRP and albumin ratio (CAO) and sodium, and a weak negative correlation between sodium/globulin ratio and CAO. This correlation between CAO and SGO may be an indication that SGO may be used in prognosis determination in the future.

In a study by Finlayson et al.[26], the mortality rate in patients over 65 years of age who were diagnosed with NSCLC and operated on was found to be lower than in patients operated on for pancreatic and esophageal malignancies. Hoy et al.[27] reported in a study that lung cancer surgery is most applicable to patients with early-stage lung cancer and is the best treatment option for patients with early-stage lung cancer. Howington et al.[28] reported that surgical resection remains the primary and preferred approach in the treatment of stage 1 and 2 NSCLC and that surgical resection reduces perioperative morbidity and mortality and increases long-term survival in patients with

early-stage lung cancer. In our study, although being operated on for lung cancer appeared to be a predictor of mortality and progression-free survival in univariate regression analysis, it was found to have no effect on mortality or progression-free survival in multiple regression analysis.

Recent studies suggest an association between diabetes and lung cancer and claim that diabetes is a risk factor for lung cancer.[29] Diabetes may affect cancer progression and prognosis through various mechanisms. Hyperglycemia has been shown to accelerate tumor metastasis and tumor progression in an animal model of lung cancer through oxidative stress.[30] Sona et al.[31] reported in a study that diabetes may adversely affect the progression of lung cancer and may be a poor prognostic factor for lung cancer. In a multicenter study, it was reported that diabetic patients with lung cancer may have a higher risk of recurrence and more invasive metastatic lung cancer. Diabetes has been shown to increase cancer invasiveness in non-small cell lung cancer through enhancement of epithelial to mesenchymal transition, which plays a key role in local tumor recurrence and metastasis.[32] Singh et al.[33] reported in a study that high insulin levels in response to insulin resistance may have an effect on cancer progression through insulin-like growth factor-1 (IGF-1). On the other hand, there are also studies indicating that diabetes has a positive effect on lung cancer. Since high levels of insulin-like growth factor 1 (IGF-1) can be carcinogenic, one study investigated the role of metformin in reducing IGF-1-mediated tumor formation and showed that metformin reduced IGF-1 levels independently of the adenosine monophosphate-activated protein kinase (AMPK) pathway. In mice treated with metformin, it has been shown that activation of the guanosine triphosphatase (GTPase)-dependent pathway and upregulation of receptor tyrosine kinase activity can significantly reduce tumor formation, independent of the reduction in IGF-1 levels.[34]

Dhillon et al.[35] found that among 409 patients with stage 1 NSCLC with diabetes mellitus, patients receiving metformin had longer survival, and metformin was an independent prognostic factor for NSCLC with diabetes mellitus. Since our patient population is small, our results may be coincidental. This result suggests that more studies are needed to clarify the role of diabetes in lung cancer. Although diabetes appeared to be a predictor of progression-free survival in univariate regression analysis, it had no effect on progression-free survival in multiple regression analysis.

CEA is one of the markers investigated for prognosis prediction in patients diagnosed with lung cancer. Nasralla et al.[36] reported in a meta-analysis of 12 studies in the literature examining the relationship between preoperative carcinoembryonic antigen (CEA) levels and survival in patients with stage 1 NSCLC that higher CEA levels were associated with higher rates of lymph node involvement and higher mortality, and that measuring preoperative CEA in patients with early-stage NSCLC may help identify patients with more advanced disease not detected by CT scan. A meta-analysis of 34 articles published in the literature by Grunnet et al.[37] found that CEA level has prognostic and predictive value in determining the risk of recurrence and mortality in NSCLC. In our study, CEA levels were higher in deceased patients compared to survivors and were not statistically significant. The CEA level of patients with progression was also not statistically significant compared to patients without progression. This is probably because our patient population was limited, the study was retrospective, and the evaluation of lymph node involvement was limited. According to a meta-analysis by Kunutsor et al.[38], there is no strong evidence that ALT has any association with cancer in general, but stratified analysis by geographic location showed an inverse association with ALT level in European populations and a positive association in Asian populations. A pooled analysis of three studies showed a strong positive association between ALT levels and cancers of the digestive tract organs. In our study, the ALT levels of patients who died may have been elevated in advanced-stage patients due to organ metastasis. However, there was no statistically significant correlation between ALT level and mortality or between progression-free survival and ALT.

Study limitations: It was a retrospective study conducted in a single institution with a relatively small number of patients; the majority of patients included in the study were advanced stage patients (which may have affected our results); and in all patients, laboratory parameters were from the pre-treatment period and results were obtained within 3 months from the date of pathologic diagnosis; however, this period was not the same for all patients, which may have affected the study.

The strength of our study: To our knowledge, this is the second study in the literature considering all cancers and the first study on lung cancer.

CONCLUSION

Laboratory parameters are advantageous because they are cheap, easily accessible, and reproducible. Among these laboratory parameters, parameters such as albumin, globulin, total protein, sodium, and CRP can be used for prognosis in cancer patients because they are associated with cancer and inflammation. However, the lack of a precise threshold value with clinical sensitivity and specificity is a problem. Although the sodium/globulin ratio was found to be insignificant in our study, it may be used as a parameter in determining cancer prognosis in the future because it is a new biomarker, significant results were found in previous literature studies, and it was associated with CAO in our study. Since there are not many studies on SGO in the literature, more experimental studies are needed to elucidate the specificity of SGO and its relationship with the etiology of lung cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 01.01.2015/01.01.2021, Decision No: 2021.06.18.).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The relationship between hepatocellular carcinoma and resolvin D1

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ABSTRACT

Aims: Liver cancer is the second most common cause of cancer death, and hepatocellular carcinoma (HCC) is the most common hepatic primary tumor. Hepatocellular carcinoma develops based on inflammation in the cirrhotic liver. The aim of our study was to determine the relationship between the decrease in Resolvin D1, the lipid mediator involved in the resolution, and hepatocarcinogenesis.

Methods: Thirty patients with HCC, thirty patients with cirrhosis, and thirty healthy subjects followed in our clinic between March 2018 and June 2019 were included in the study. Routine laboratory test results of the patients were recorded from the institutional database. Resolvin D1 and other parameters of the study groups were compared.

Results: The Resolvin D1 levels were found to be significantly different from each other group, with the ranking as follows: the HCC group (1.71±1.46 ng/ml) <the cirrhotic group (3.63±2.92 ng/ml) <the healthy control group (6.24±3.18 ng/ml) ($p<0.001$). Moreover, Resolvin D1 levels were negatively correlated with α-fetoprotein (AFP) level and tumor stage ($p<0.001$).

Conclusion: Reduced lipid mediators that aid in the resolution process cause an increase in pro-inflammatory cytokines involved in the development of hepatocellular carcinoma. A decrease in Resolvin D1 may serve as a biomarker contributing to the diagnosis of progression to HCC in cirrhotic patients by triggering chronic inflammation and hepatocarcinogenesis.

Keywords: Hepatocellular carcinoma, cirrhosis, pro-inflammatory cytokines, AFP, Resolvin D1

INTRODUCTION

Liver cancer is the fifth most common cancer globally and second in cancer-related deaths. Hepatocellular carcinoma (HCC) accounts for about 90% of liver cancers. Most patients are diagnosed at an advanced stage, resulting in limited treatment options and lower chances of successful treatment. Five-year survival is about 30-50% in patients with HCC.[1]

Cirrhosis is present in 90% of patients diagnosed with hepatocellular carcinoma.[2] The most common causes of cirrhosis are viral hepatitis and alcohol.[3] It is recommended that patients in the risk group should be screened regularly by α-fetoprotein (AFP) and ultrasonography (USG) in order to make an early diagnosis of HCC.[4] AFP is a biomarker released from cancer stem cells and is used in early diagnosis.[5]

In the cirrhotic liver, metabolic and oxidative damage due to inflammation, necrosis, and recurrent compensatory regeneration occur through pro-inflammatory cytokines. As a result, accumulated point mutations and genetic errors cause suppression of tumor suppressor genes and activation of proto-oncogenes.[3]

Special lipid mediators are involved in the resolution pathways, which represents an inflammatory response's ideal outcome. Disorders or deficiencies in the pathways associated with these lipid mediators are involved in the pathogenesis of chronic inflammatory diseases and tumors that develop due to prolonged inflammation.[6]

The lipid mediator responsible for resolution, Resolvin D1, is synthesized from doxhexanoic acid via lipoxygenase or aspirin-acetylated COX-2. Resolvin D1, through the activation of ALX/FPR2 and GPR32 receptors, lowers endothelial-neutrophil interaction, actin polymerization induced by LTB4, and the expression of CD11b, which is responsible for adhesion. Thus, it prevents the transendothelial migration of PMNL. Resolvin D1 increases the phagocytosis (efferocytosis) of apoptotic leukocytes, bacteria, and yeast particles in monocytes/mature macrophages.[7]

Resolvin D1 reduces IL-8-induced neutrophil chemotaxis. It stimulates antibody-secreting B-cell differentiation. It also reduces pro-inflammatory cytokines released from endothelial cells.[8]

Resolvin D1 also regulates the polarization of macrophages at the site of inflammation, allowing the macrophages in the M1 (pro-inflammation) pathway to convert to the M2 (anti-inflammation) pathway.[9] Thus, Resolvin D1 is effective in both ameliorating inflammation (reduces PMNL infiltration) and resolution (increases efferocytosis). It reduces necroinflammatory liver damage by reducing DNA damage and oxidative radicals in hepatocytes. A decrease in Resolvin D1 triggers both chronic inflammation and the formation of hepatocarcinogenesis via pro-inflammatory cytokines.[7]

In this study, we aimed to determine the role of Resolvin D1 in the pathogenesis of hepatocellular carcinoma and compare its levels along with AFP in cirrhotic patients with hepatocellular carcinoma, and patients with cirrhosis only and to those of healthy individuals.

METHODS

Thirty patients with hepatocellular carcinoma, thirty patients with liver cirrhosis, and thirty subjects without known health problems who were followed in the Gastroenterology Clinic of Kırıkkale University Medical Faculty Hospital were included in the study between patients and healthy individuals who accepted and signed the informed consent form participated in the study. The study was approved by the Clinical Researches Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 19/03/2019, Decision No: 06/03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The diagnosis of HCC is based on the guidelines of the European Society for Research on Liver Diseases (EASL), imaging methods (ultrasonography, magnetic resonance imaging, computed tomography), and biochemical values (AFP and liver function tests). Patients with hepatic disease other than hepatocellular carcinoma and cirrhosis, liver metastasis, or other malignancy were excluded.

Imaging methods and clinical and laboratory findings showing portal hypertension were used to diagnose cirrhosis. Individuals with chronic inflammatory diseases such as diabetes mellitus, chronic kidney disease, and collagen tissue disease, and patients who had acute infection were excluded from the healthy control group without known liver disease and alcohol use.

Blood samples were obtained from the patients included in the study after fasting for at least 12 hours. Blood samples were separated from those taken for routine tests, taken into two cc tubes, and stored in a -80°C freezer. Serum AFP levels were determined by chemoluminescence method using a cobas® e601 device and original Roche diagnostic kits. Resolvin D1 levels were assayed using the original ELISA kit (Human RvD1 ELISA kit, SUNRED). Resolvin D1 was measured quantitatively via colorimetric analysis using a spectrophotometer.

Statistical Analysis

Statistics software (SPSS 18 for windows, IBM Co., Chicago, Il, USA) is used for statistical analyses. Normality analysis of the study variables was conducted with Shapiro Wilk test.

Kruskall Wallis test was used for statistical analysis of nonparametric study findings, and $p<0.05$ was considered statistically significant. Mann-Whitney U test and Bonferroni Correction test were used in paired group comparisons, and $p<0.017$ was considered statistically significant. Non-parametric variables were expressed as medians (min-max).

The parametric study variables were analyzed using a One Way Analysis of Variance (ANOVA) test, with a significance level of $p<0.05$. Tukey Multiple Comparisons test was used in paired group comparisons, and $p<0.05$ was considered significant. These variables were expressed as means and standard deviations.

In addition, Pearson's correlation test was used to determine the correlation between the parameters of the patients.

The ROC-Curve test was used to determine the predictive characteristics of the study parameters to differentiate the disease, and the sensitivity and specificity ratios of the parameters to distinguish the disease were determined by obtaining "cut-off" values. In addition, the Logistic Regression test and Likelihood Ratio test were used to determine which of these parameters might be the best parameter for differentiation of the disease. The $p<0.05$ was considered statistically significant.

RESULTS

Thirty HCC patients, thirty cirrhosis patients, and thirty healthy people were included in the study. When the demographic characteristics of the participants were examined, it was seen that the healthy group mainly consisted of female patients, and the cirrhosis and HCC groups consisted mostly of male patients. There was no significant difference between the three groups in terms of age ($p=0.544$) (Table 1).

Considering the etiology of 60 patients included in our study, of the 30 patients in the HCC group, 17 (56.7%) were HBV, 10 (33.3%) were NASH, and the remaining 3 (10.0%) were HCV. Of the 30 patients in the cirrhosis group, 16 (53.3%) were HBV, 11 (36.7%) were NASH, 2 (6.7%) were HCV, and the remaining 1 (3.3%) had possible autoimmune etiology (Table 1).

Of the 30 patients in the HCC group, 11 (36.7%) were stage I, 10 (33.3%) were stage IIIA, 5 (16.7%) were stage IIIB, and 4 (13.3%) were stage IVB. The mean tumor size was 6.1±4.8 cm (median: 5.2; min-max: 1-22.5) (Table 1).

According to the Child-Pugh classification, 18 (60.0%) of the 30 patients in the HCC group were classified as A, 9 (30.0%) as B, 3 (10.0%) as C; of the 30 patients in the cirrhosis group, 22 (73.3%) were classified as A, 6 (20.0%) as B and 2 (6.7%) as C (Table 1).

Of the 30 patients in the HCC group, 19 (63.3%) had no acid, 3 (10.0%) had perihepatic acid, and 8 (26.7%) had common acid. Of the 30 patients in the cirrhosis group, 24 (80.0%) had no acid, and 6 (20.0%) had common acid. There was no significant difference in acidity between HCC and cirrhosis groups ($p=0.152$) (Table 1).

After the analysis applied to the patient data, Resolvin D1 ($X^2=32,927$, **$p<0.001$**), and AFP ($X^2=42,763$, $p<0.001$) were statistically different between the three groups (Table 2).

Table 1. Characteristics of participants

VARIABLE	HCC (n=30)	Cirrhosis (n=30)	Control (n=30)	Test and p-value
	n (%)			
Gender				
Female	5 (16.7)	12 (40.0)	22 (73.3)	X^2=19.819*
Male	25 (83.3)	18 (60.0)	8 (26.7)	**p<0.001**
	Average ± SD (min-max)			Test and p-value
Age (year)	62.9 ± 8.6 (45-79)	60.8 ± 11.0 (34-88)	60.5 ± 7.0 (51-78)	F=0.613 p=0.544**
Etiology				-**
NASH	10 (33.3)	11 (36.7)		
HBV	17 (56.7)	16 (53.3)		
HCV	3 (10.0)	2 (6.7)		
Autoimmune	-	1 (3.3)***		
Stage		-		-
I	11 (36.7)			
IIIA	10 (33.3)			
IIIB	5 (16.7)			
IVB	4 (13.3)			
Child-Pugh				-****
A	18 (60.0)	22 (73.3)		
B	9 (30.0)	6 (20.0)		
C	3 (10.0)	2 (6.7)		
Acid				X^2=2.052
No	19 (63.3)	24 (80.0)		p=0.152*****
Perihepatic	3 (10.0)	-		
Common	8 (26.7)	6 (20.0)		

** One-way ANOVA was performed
*** Possible autoimmune etiology
**** The test could not be performed because the expected values did not meet the Chi-square test assumptions.
***** Acid variable is re-interpreted as existent and non-existent, and then Fisher's exact test is performed

Table 2. Biochemical values

Variable	HCC Average ± SD (min-max)	Cirrhosis Average ± SD (min-max)	Control Average ± SD (min-max)	Test (F/X2) **	p-value*
AFP (ng/ml)	43.59±716 (1.40-3340)	4.46±3.255 (1.48-16.02)	2.44±1.44 (0.84-6.46)	42.763	**<0.001**
Resolvin D1 (ng/ml)	1.71±1.46 (0.28-6.05)	3.63±2.92 (0.56-11.90)	6.24±3.8 (2.35-13.45)	32.927	**<0.001**

* One Way Analysis of Variance, (ANOVA) test, Kruskal Wallis test, p <0.05
** F value

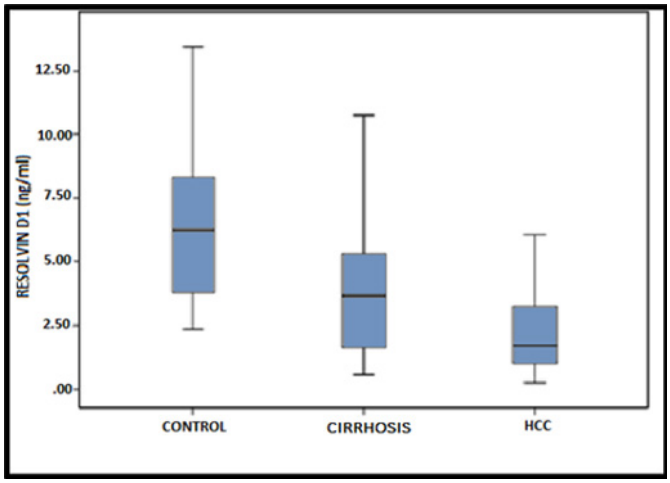

Figure 1. Distribution of Resolvin D1 levels by groups

Resolvin D1 levels were significantly different between the control and cirrhosis group (Z=-3.046, **p=0.002**), control and HCC group (Z=-5.611, **p<0.001**), and cirrhosis and HCC group (Z=-2.898, **p=0.004**). With these findings, Resolvin D1 levels were highest in the control group and lowest in the HCC group (Figure 1).

AFP levels differed between control and cirrhosis groups (Z=-3.534, **p<0.001**), control and HCC groups (Z=-5.604, **p<0.001**), and cirrhosis and HCC groups (Z=-4.716, **p<0.001**). The AFP levels were found to be the lowest in the control group and the highest in the HCC (Figure 2).

There was a significant difference between the three groups in terms of gender, resolvin D1 levels and AFP values (Table 3).

At the end of the correlation analysis, a negative correlation was found between Resolvin D1 and AFP (r=-0.429, p<0.001) and Resolvin D1 and tumor stage (r=-0.509, p<0.001). It is thought that Resolvin D1 level could be found as low while AFP level or tumor stage increases.

On the other hand, there was a positive correlation between AFP and acid form (r=0.236, **p=0.025**), AFP, and tumor stage (r=0.625, **p<0.001**). It is thought that if the AFP level is measured as high, there is the possibility of widespread acidity in the patients, and the current stage of the tumor may be increased if the patient has a tumor.

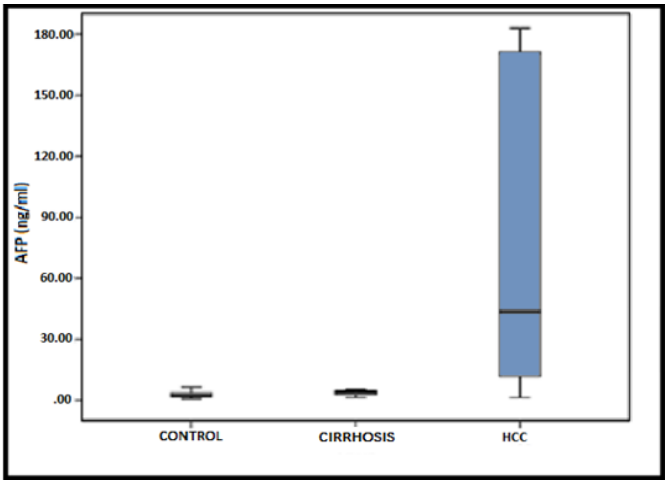

Figure 2. Distribution of alpha-fetoprotein levels by groups

Table 3. Evaluation of differences between groups

Variable	Group	Mean Difference / Z	p
Gender (F=1 M=2)	Control / Cirrhosis	-2.583	**0.010**
	Control / HCC	-4.375	**<0.001**
	Cirrhosis / HCC	-1.989	**0.047**
Resolvin D1	Control / Cirrhosis	-3.046	**0.002**
	Control / HCC	-5.611	**<0.001**
	Cirrhosis / HCC	-2.898	**0.004**
AFP	Control / Cirrhosis	-3.534	**<0.001**
	Control / HCC	-5.604	**<0.001**
	Cirrhosis / HCC	-4.716	**<0.001**

(*) mean difference value, Tukey Multiple Comparisons test, Mann-Whitney U test, p <0.05

At the end of the ROC-Curve test, it is predicted that when Resolvin D1 value<2.64 (area =0.271, **p=0.002**, sensitivity 67%, specificity 93%) and AFP value>2.91 (area=0.766, **p<0.001**, sensitivity 80%, specificity 70%), these parameters could differentiate cirrhosis patients from the control group (Table 4).

Table 4. Specificity and sensitivity of the parameters of the groups

Group	Variable	Area	p	Cut-off	Sensitivity	Specificity
Control-Cirrhosis	RESOLVİN D1	0.271	**0.002**	<2.64	%67	%93
	AFP	0.766	**<0.001**	>2.91	%80	%70
Control-HCC	RESOLVİN D1	0.078	**<0.001**	<2.46	%74	%96
	AFP	0.921	**<0.001**	>4.31	%83	%83
Cirrhosis-HCC	RESOLVİN D1	0.282	**0.004**	< 3.41	%84	%60
	AFP	0.854	**<0.001**	> 5.63	%80	%84

ROC curve test, p<0.05

At the end of the ROC-Curve test, it is predicted that when Resolvin D1 value<2.46 (area=0.078, **p<0.001**, sensitivity 74%, specificity 96%) and AFP value>4.31 (area=0.921, **p<0.001**, sensitivity 83%, specificity 83%), these parameters could differentiate HCC patients from healthy patients (Table 4).

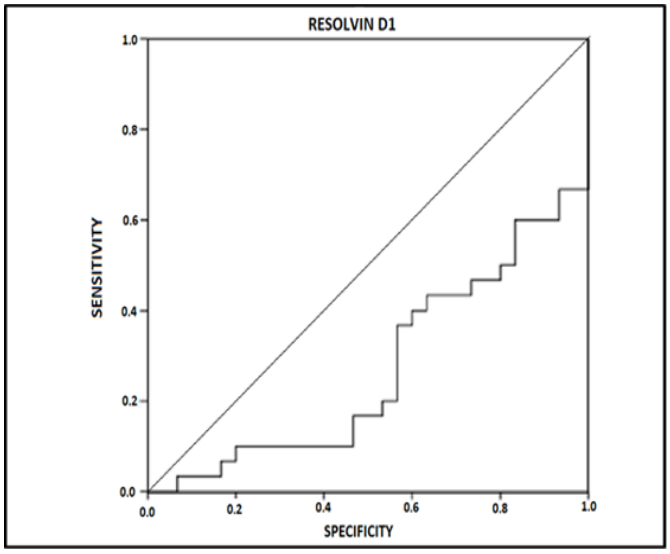

Figure 3. ROC-Curve graph of Resolvin D1 variable which can differentiate cirrhosis patients from control group

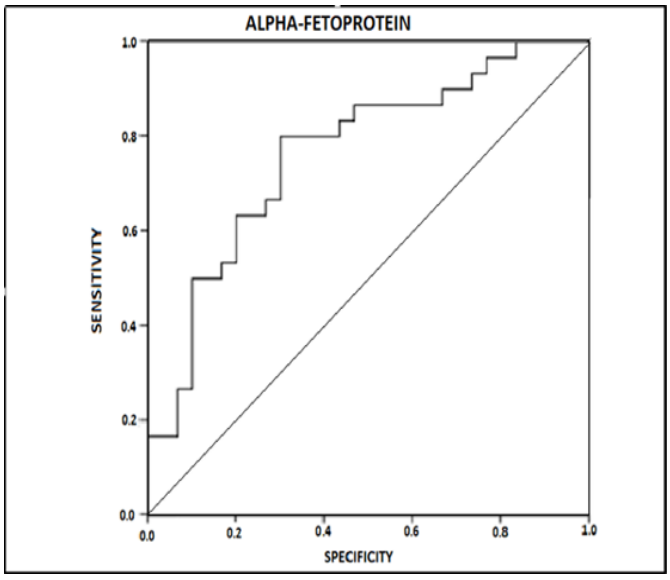

Figure 4. ROC-Curve graph of alpha-fetoprotein variable that can differentiate cirrhosis patients from control group

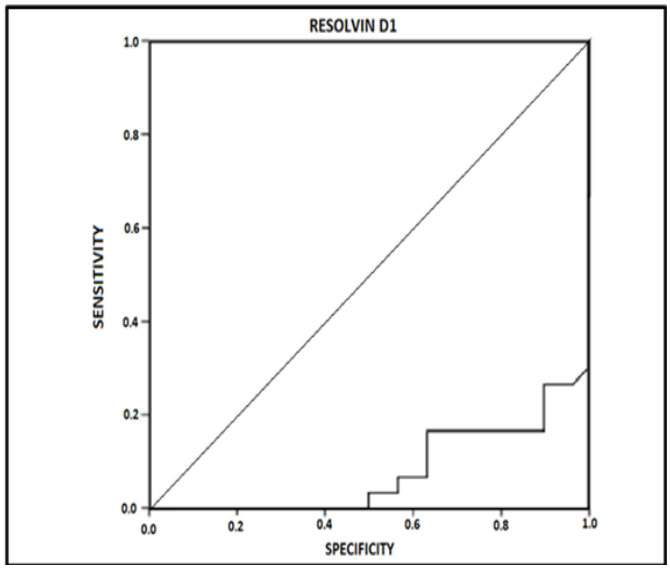

Figure 5. ROC-Curve graph of Resolvin D1 variable that can differentiate HCC patients from healthy subjects

At the end of the ROC-Curve test, it is predicted that when resolvin D1 value<3.41 (area=0.282, p=0.004, sensitivity 84%, specificity 60%) and AFP value>5.63 (area=0.854, p<0.001, sensitivity 80%, specificity 84%), these parameters could differentiate HCC patients from cirrhosis patients (Table 4).

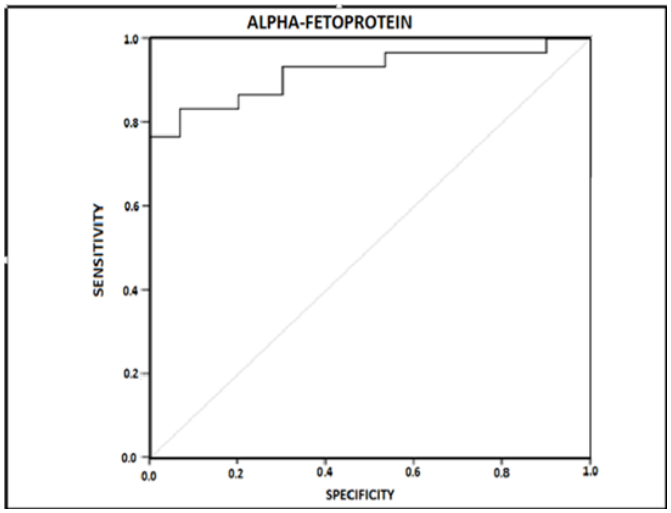

Figure 6. ROC-Curve graph of alpha-fetoprotein variable that can distinguish HCC patients from cirrhosis patients

DISCUSSION

Our study revealed significant statistical differences in the level of Resolvin D1 between the HCC and control groups, cirrhosis and control groups, and the HCC and cirrhosis groups. Specifically, Resolvin D1 levels were lower in the HCC group than the cirrhosis group and lower in the cirrhosis group than the control group. Furthermore, a negative correlation was observed between the degree of inflammation and the level of Resolvin D1. Our findings indicate a gradual decline in Resolvin D1 levels during the progression of inflammation and the development of carcinogenesis.

In our study, all patients diagnosed with hepatocellular carcinoma exhibited cirrhotic liver, and the leading etiologies of both conditions were chronic HBV infection, NASH, and chronic HCV infection. Correspondingly, Akinyemiju and colleagues 10 reported that HBV infection accounted for approximately 54% of HCC cases, while HCV infection and other causes accounted for 31% and 15%, respectively. Our study also revealed chronic HBV infection as the most common cause of HCC, and this was consistent in both Africa and East Asia. However, in Western countries, HCV infection is the predominant cause.[10]

It is known that pro-inflammatory cytokines are increased, and mediators related to resolution decrease in chronic inflammatory diseases and tumor microenvironments.[11] Navarini et al. found that in 30 patients with systemic lupus erythematosus (SLE), the Resolvin D1 level is lower than in the healthy group.[12] Fedirko et al.[13] showed that there was no association with Resolvin D1 in patients with colon adenoma in their first human study of 200 patients. Conversely, Morshedzadeh and colleagues 14 reported lower levels of Resolvin D1 in 60 patients with polycystic ovary syndrome compared to healthy individuals, with a corresponding development of subclinical inflammation. Zhuang and colleagues 15 discovered that inflammatory cytokines were elevated and Resolvin D1 levels were reduced in 50 individuals with colon cancer. Moreover, they observed a decrease in Resolvin D1 levels in correlation with the advancement of the cancer stage. Similarly, in patients with metastatic liver cancer, Resolvin D1 levels were found to be low in the early period after resection and raised in the late period.[16]

There are many experimental studies on Resolvin D1. Kuang et al.[17] showed in a study with mice that Resolvin D1 reduces inflammatory cytokines (TNF-α, IFN-γ, IL-2, IL-1β, and IL-6) and NF-κB signaling in concanavalin-induced liver cancer. Sulciner et al.[18] reported that cell debris caused by cytotoxic chemotherapy in lung cancer is increased clearance with Resolvin D1 and may be used in addition to cytotoxic chemotherapy.

Kang et al.[19] found that Resolvin D1 reduces pro-inflammatory cytokines in ischemic liver injury and changes macrophage polarization from the M1 pathway to the M2 pathway. Lee et al.[20] showed that Resolvin D1 reduces metastasis and inhibits TGF-β1 via its ALX/FPR2 and GPR32 receptors in lung cancer. Deyama et al.[21] found anti-depressant effects of Resolvin D1 in lipopolysaccharide-induced depression models. Collectively considering our study alongside other experimental studies, we can gain a more comprehensive understanding of the role and significance of Resolvin D1 in the pathogenesis of hepatocellular carcinoma.

The cirrhotic process represents a significant predisposing factor for developing hepatocellular carcinoma, highlighting the need for close monitoring of cirrhotic patients to facilitate early detection of HCC. Previous studies have demonstrated a negative correlation between alpha-fetoprotein (AFP) levels and the prognosis of HCC 22,23, whereas Yan and colleagues 24 observed a positive correlation between AFP levels and the development and tumor stage of HCC in a cohort of 24 HCC and 62 HBV-related liver cirrhosis patients. AFP protein is a valuable diagnostic tool for identifying hepatocellular carcinoma in cirrhotic and healthy populations. Our study results suggest that AFP measurements can effectively distinguish between the HCC and cirrhosis group, HCC and control group, and cirrhosis and control groups (p<0.001). Furthermore, we observed a negative correlation between tumor stage and AFP levels with Resolvin D1, indicating that decreased Resolvin D1 could serve as a critical indicator for both the diagnosis and progression of hepatocellular carcinoma.

Our study found no significant difference in the Child-Pugh scores between cirrhotic patients and those with HCC. However, we did observe lower levels of Resolvin D1 in patients with HCC compared to those with cirrhosis, providing further evidence for the involvement of Resolvin D1 in the development of hepatocellular carcinoma. Regarding diagnostic accuracy, our study found that AFP protein had a sensitivity and specificity of 83% and 83%, respectively, in distinguishing the HCC group from the control group. Meanwhile, Resolvin D1 had a sensitivity and specificity of 74% and 96%, respectively. The sensitivity and specificity of AFP protein were found to be 80-84% and 84-60%, respectively, in differentiating the cirrhosis and HCC groups. In contrast, the sensitivity and specificity of Resolvin D1 were 84-60%, respectively. Although Resolvin D1 was the best parameter in differentiating the healthy and HCC groups in our study, AFP was more effective in differentiating the cirrhosis and HCC groups, as well as the healthy and cirrhosis groups.

Study limitations: Our study is the first clinical study to reveal the relationship between resolution pathways and

hepatocellular carcinoma. However, further clinical trials with larger patient populations are required to determine the exact role of Resolvin D1 in the pathogenesis of HCC. The limited number of patients is one of the limitations of our study. The sample size in our study was relatively small, which may limit the generalizability of our findings. A larger sample size would have allowed for a more robust statistical analysis and increased the power to detect significant associations between Resolvin D1 levels and HCC. Furthermore, our study only measured Resolvin D1 levels at a single time point. This cross-sectional design does not provide information on the temporal relationship between Resolvin D1 levels and HCC development or progression. Longitudinal studies with repeated measurements of Resolvin D1 would provide more comprehensive insights into the association between Resolvin D1 and HCC. Moreover, our study did not assess other potential confounding factors that may influence the relationship between Resolvin D1 and HCC, such as genetic predisposition, lifestyle factors, or comorbidities. The lack of adjustment for these variables may have limited our ability to fully evaluate the true association between Resolvin D1 and HCC. Lastly, the measurement of Resolvin D1 itself may have certain limitations. The assays used to quantify Resolvin D1 levels may have inherent variability and measurement error. Additionally, Resolvin D1 metabolism and clearance rates may vary among individuals, which may have influenced the observed levels in our study population. Overall, while our study provides preliminary insights into the relationship between Resolvin D1 levels and HCC, these limitations should be recognized and taken into consideration when interpreting the results. Future studies with larger sample sizes and comprehensive adjustment for potential confounding factors are needed to further elucidate this relationship.

CONCLUSION

Our study found that Resolvin D1 is the most influential parameter for distinguishing individuals with HCC from healthy individuals. We also found a negative correlation between Resolvin D1 levels and both AFP level and tumor stage. These findings suggest that Resolvin D1 could be a valuable tool for predicting the development of HCC in patients with cirrhosis. However, further long-term prospective studies involving larger patient populations are needed to fully understand the diagnostic and prognostic potential of Resolvin D1 in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Researches Ethics Committee of the Kırıkkale University Faculty of Medicine (Date: 19/03/2019, Decision No: 06/03).

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Case Report

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Autoimmune hemolytic anemia associated with clear cell renal carcinoma: a case report

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ABSTRACT

Autoimmune hemolytic anemia (AIHA) is hemolytic anemia characterized by auto-antibodies against erythrocytes. It is commonly induced by hematological neoplasms such as malignant lymphoma; however urological cancers are rarely seen in this area. We present a case of clear cell renal carcinoma that responded to right partial nephrectomy, presenting with Coombs-positive warm AIHA. A 34-year-old male patient presented with fatigue lasting for 1 week, and icterus. His hemoglobin level was 6.8 g/dL, indirect bilirubin was 9.3 mg/dL, lactate dehydrogenase (LDH) 1031 U/L and both direct and indirect Coombs tests were positive. In the abdominal computed tomography, there was a 6 cm diameter mass lesion of heterogeneous density in the middle part of the right kidney. Corticosteroid treatment was started and then partial nephrectomy was performed. After surgical resection, the hemoglobin level gradually returned to normal. We detected warm AIHA associated with clear cell renal cancer. We are reporting on clear cell renal cancer that responded to corticosteroids and partial nephrectomy, presenting with severe AIHA at the hematology clinic. Clear cell renal cancer should be considered in the differential diagnosis for warm AIHA, and nephrectomy might offer a treatment option for renal cell carcinoma associated AIHA.

Keywords: Autoimmune hemolytic anemia, clear cell renal carcinoma, partial nephrectomy, paraneoplastic syndrome

INTRODUCTION

Paraneoplastic syndromes (PNSs) have been recognized as a variety of symptoms associated with certain cancers but not directly attributable to tumor invasion or compression. PNSs are linked to tumor secretion of functional peptides and hormones or to immune cross-reactivity between tumor and normal host tissues. These syndromes can affect various organ systems, including the neurological, hematological, endocrinological, dermatological, and rheumatological systems. Autoimmune hemolytic anemia can be seen as a paraneoplastic syndrome. It has been reported that treatment of the underlying tumor usually improves such conditions.[1,2]

CASE

A 34-year-old male patient presented with complaints of weakness, yellowing of the eyes and skin for 1 week. On physical examination, the sclera and skin were distinctly yellow. Hemoglobin level was 6.8 g/dl (normal, 13.5-16.5 g/dl), mean erythrocyte volume (MCV) was 105.8 fL, leukocyte counts was 7.85 x 10^3/ul and platelet count was 430 x 10^3/µl. Absolute reticulocyte count was high as 6.97%. Prothrombin time and activated partial thromboplastin time were within normal time intervals. The serum haptoglobin level was normal, at 1.36 mg/dl. While lactate dehydrogenase level increased to 1031 U/L (normal, 0-450 U/L), serum total bilirubin level increased significantly to 10.3 mg/dl (normal, 0.0-1.1 mg/dl), and the direct bilirubin level was slightly elevated 1 mg/dl (normal, 0.0-0.4 mg/dl). The patient's iron level was 169 µg/dl (50-178 µg/dl), total iron binding capacity was 153 µg/dl (173-285 µg/dl), transferrin was 52% (16-45), ferritin level was 287.12 ng/ml, folate level was 2,7 ng/ml (3.1-19.9 ng/ml), and B12 level was 225 pg/ml (187-883 pg/ml). It was observed that B12 level was normal and folate level was low. Serum immunoglobulin (Ig) levels were normal and no abnormal band was detected in electrophoresis. While the direct Coombs test was positive for IgG and complement C3, the indirect Coombs test was also positive. The other tests to exclude other autoimmune diseases; anti-nuclear antibodies, antibodies against double-stranded DNA, and anti-phospholipid antibodies were all negative. Crossmatch compatible blood transfusion was given to the patient. The patient's weight was 80 kg. Therefore, oral corticosteroid therapy 80 mg/day (1 mg/kg) was administered after the diagnosis was made, resulting in limited improvement.

Abdominal, thorax and neck computed tomography scans were requested in order to diagnose the underlying malignant lymphomas. On the abdominal computed tomography, there was a 6 cm diameter mass lesion of heterogeneous density in the middle part of the right kidney and it was confirmed by magnetic resonance imaging. Right partial nephrectomy was planned as the surgical treatment and clear cell renal carcinoma was reported through the pathology result. After right partial nephrectomy, hemoglobin levels and reticulocyte count gradually returned to normal. Full body computerized tomography scans with neck, abdomen and thorax were taken 6 months after the operation for surveillance. There were no findings that reveals malignancy other than the serous collection area in the operation area. The direct Coombs test was positive for IgG and complement C3, while the indirect Coombs test was negative.

DISCUSSION

AIHA is a disease caused by auto-antibodies against erythrocytes. Most cases of AIHA are idiopathic, but AIHA may be secondary to some malignancies. These immune-mediated hematological diseases are uncommon but can be seen as a typical PNS. In the literature, AIHA as a PNS has been diagnosed with a variety of multiple tumors, including hematological neoplasms such as malignant lymphoma, squamous cell carcinoma, adenocarcinoma, renal cell carcinoma, small cell carcinoma, and seminoma. However, renal malignancy is rarely associated with hematological PNS.[3,4]

AIHA developing secondary to the paraneoplastic process of the renal tumor has been reported to be associated with severe anemia, which can lead to serious morbidity and even mortality.[5] In this respect, accurate diagnosis of AIHA as PNS and initiation of treatment as soon as possible is vital. The diagnosis of paraneoplastic AIHA should be made after exclusion of metastases, infections, metabolic processes, and vascular changes. The pathogenesis of these PNSs includes the release of substances with endocrine and metabolic activity by tumor cells or induction of the release of inflammatory mediators, particularly cytokines such as interleukin (IL).[3] Steroids represent the main treatment for idiopathic AIHA. Although other immunosuppressants such as azathioprine, mycophenolate mofetil, monoclonal antibodies rituximab and intravenous immunoglobulins have also been used successfully, steroid-resistant cases may also require splenectomy. Control of carcinoma by tumor excision, corticosteroids, other immunosuppressant agents and chemotherapy may improve hematological abnormalities. In fact, most reports about kidney tumors seem to be identified with nephrectomy as an effective treatment.[6,7]

In our case, we performed partial nephrectomy to completely control AIHA that partially responded to corticosteroid treatment and for primary treatment of renal cancer. Surgical treatment improved the hemolytic status and corticosteroid treatment was discontinued with a controlled taper. There was no recurrence. There was no finding in favor of metastasis in the control tomography. This demonstrates the importance of surgery in conjunction with steroid therapy for the control of AIHA.

In addition, the fact that the patient's direct Coombs test is still positive may be attributed to the metastasis due to clear cell kidney cancer or the received erythrocyte replacement. Continuation of corticosteroids or use of immunosuppressant agents such as rituximab were not considered due to normal Hg and reticulocyte levels. The patient is under close follow-up.

CONCLUSION

We report a rare case of AIHA as a PNS associated with clear cell renal cancer. As a PNS, hemolytic anemia is diagnosed by excluding other causes such as primary hematological changes, metastasis, and vascular processes. Hemolytic anemia might be considered as a PNS in patients presenting with AIHA and may be associated with the cases of clear renal cell cancer. It should be kept in mind that surgical intervention is considered together with steroid administration in these patients.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written permission is available for review by the editor of this journal.

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Case Report

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Ponatinib-induced dilated cardiomyopathy: a case report.

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ABSTRACT

Ponatinib is a third-generation tyrosine kinase inhibitor with potent efficacy in the treatment of acute and chronic leukemia. Despite having an effective and sustained activity in all BCR-ABL1 mutations, it may cause cardiovascular adverse effects. Here we report a 56-year-old male patient with Chronic myeloid leukemia and no prior cardiac disorder who developed acute heart failure under ponatinib treatment. Guideline-recommended medical treatment for heart failure was initiated. Coronary angiography to exclude ischemic heart disease revealed no coronary stenosis. Cardiac magnetic resonance imaging showed findings consistent with non-ischemic dilated cardiomyopathy. After interruption of ponatinib treatment, cardiac evaluation showed improvement in left ventricular ejection fraction. Patients on Ponatinib therapy should be closely monitored for signs and symptoms of heart failure.

Keywords: Cardio-oncology, dilated cardiomyopathy, heart failure

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by increased tyrosine kinase activity.[1] Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of CML. So far, multiple TKIs have been approved for the treatment of CML; however, TKI-related toxicities have long been known.[2] Ponatinib is a third generation TKI was approved by US Food and Drug Administration for CML in cases of resistance or intolerance to prior TKI therapy.[3] In this report, we present a 56-year-old male patient with CML and no prior cardiac disease who developed dilated cardiomyopathy after treatment with ponatinib.

CASE

A 56-year-old male patient presented with postprandial abdominal pain, diffuse abdominal tenderness, and new-onset bilateral lower extremity edema. The patient was diagnosed with CML in 2017 and treated with TKIs including imatinib, dasatinib, and nilotinib, however failed to achieve molecular and clinical response. As a result, the patient was switched to ponatinib due to resistant disease despite previous TKI treatments. After starting at a daily dosage of 45 mg, the patient achieved molecular and clinical response and has subsequently been maintained on a daily dose of 15 mg of ponatinib for four years. The patient's initial laboratory results indicated acute kidney injury with a creatinine value of 1.44 mg/dl. Additionally, the level of liver enzymes were elevated with alanine aminotransferase at 632 U/L, aspartate aminotransferase at 437 U/L, alkaline phosphatase at 418 U/L, gamma-glutamyl transferase at 399 U/L, and total bilirubin at 3.98 mg/dl. Abdominal ultrasound revealed no abnormalities, except for hepatomegaly. The concentration of brain natriuretic peptide was measured at 3227.2 pg/ml. Hepatic congestion and cardiorenal syndrome secondary to heart failure was suspected. Transthoracic echocardiography revealed a significant decrease in the ejection fraction (EF) to 25% compared to the patient's baseline EF of 55% before initiating ponatinib treatment. Ponatinib treatment was discontinued and replaced with guideline-recommended medical therapy consisting of ramipril 5 mg/day, spironolactone 25 mg/day, carvedilol 6.25 mg/day, and twice-daily administration of 40 mg of intravenous loop diuretic. A coronary angiogram was conducted to rule out ischemic heart disease, but no significant stenosis was detected. Cardiac magnetic resonance imaging (CMR) showed mid-myocardial fibrosis in the septum, contrast uptake in the papillary muscles at the basal segments, and diffuse interstitial fibrosis in other myocardial segments consistent with non-ischemic dilated cardiomyopathy (Figure). During hospitalization, there was an improvement in creatinine levels and liver

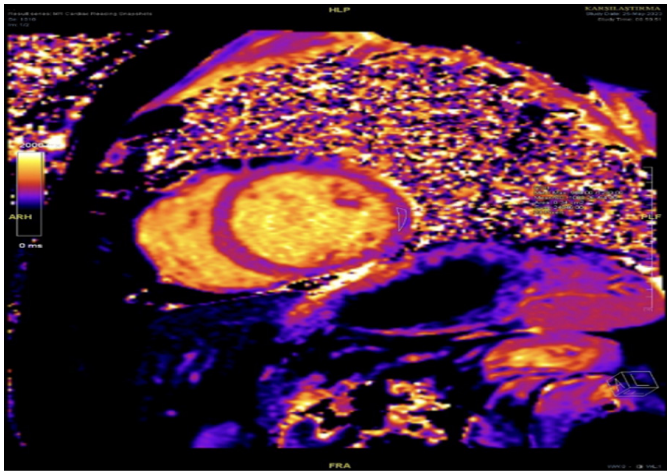

Figure. Cardiac magnetic resonance imaging (CMR) reveals mid-myocardial fibrosis in the septum, contrast uptake in the papillary muscles at the basal segments, and diffuse interstitial fibrosis in other myocardial segments.

enzymes, and the hypervolemic condition resolved. Follow-up echocardiography revealed the recovery of left ventricular function with an ejection fraction of 50%. The patient was discharged for continuation of current medical treatment and close follow-up. In the last visit, he was deemed ineligible for a stem cell transplantation due to several comorbidities. At present, the patient is not currently receiving any TKI and is being closely monitored on a monthly basis.

DISCUSSION

Dilated cardiomyopathy is defined as the presence of left ventricular dilatation and global or regional systolic dysfunction unexplained solely by abnormal loading conditions (hypertension, valvular disease, congenital heart disease) or coronary artery disease. According to the recently published 2023 European Society of Cardiology Cardiomyopathy Guideline, contrast enhanced CMR is recommended in all patients with suspected cardiomyopathy at initial evaluation.[4] In our patient, the absence of ischemic heart disease assessed through invasive angiography, the absence of valvular and congenital heart disease assessed through echocardiography, and the presence of left ventricular dilatation and systolic dysfunction, along with interstitial fibrosis and late gadolinium enhancement documented by cardiac MRI, indicated a "ponatinib-related dilated cardiomyopathy phenotype with midmyocardial fibrosis and low EF". Laboratory and clinical improvement after withdrawal of the implicated agent also supported the diagnosis.

Cardiovascular (CV) adverse events are considered common complications of ponatinib treatment. The safety of ponatinib have been evaluated in the Ponatinib Philadelphia chromosome–positive acute lymphoblastic leukemia and CML Evaluation.[5] The study highlighted the risk of arterial occlusion and CV adverse events in general in ponatinib-treated patients and shown that reducing the dose of ponatinib in certain settings can achieve optimal responses and reduce ponatinib-related CV events.[5,6] Pharmacokinetic analysis has indicated the possibility of reducing the starting dose of ponatinib to 15 mg/day and preliminary data showed advantages in terms of safety while maintaining its efficacy.[6]

Mechanisms leading to ponatinib cardiotoxicity are still not fully understood. Ponatinib is a potent inhibitor of various tyrosine kinases, including FGFRi, PDGFR and VEGFR.[7] Some studies suggested that multi-kinase inhibitor properties of ponatinib may play a role in cardiovascular complications by causing endothelial dysfunction.[8-10] Some in-vivo studies have demonstrated that ponatinib impairs AKT and ERK pathways which are important for cardiomyocyte survival.[11,12] Ponatinib associated inhibition of AKT and ERK pro-survival pathways and disruption of cardiac cells leads to left ventricle dysfunction and heart failure.[12] So, it is considered that ponatinib induced heart failure may be reversed after stopping ponatinib treatment, patients should be closely monitored for signs and symptoms of congestive heart failure.[13]

CONCLUSION

Ponatinib is associated with cardiac adverse events including vascular occlusion, myocardial infarction, and left ventricular dysfunction. Herein, we reported a patient developed dilated cardiomyopathy while receiving low dose ponatinib. To our knowledge, this is first case reported with dilated cardiomyopathy as an adverse event of ponatinib.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from the patients for the publication of the case report and accompanying images.

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Case Report

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Hereditary hyperferritinemia cataract syndrome with iron deficiency : a case report

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ABSTRACT

Hereditary hyperferritinemia-cataract syndrome (HHCS) is a rare disease characterized by high serum ferritin levels, congenital bilateral cataracts, and the absence of tissue iron overload. HHCS is an autosomal dominant inherited rare genetic disease. In this case report, we aimed to present a young female patient with a history of cataracts in herself and her family members. Our patient had the dilemma of iron deficiency anemia and hyperferritinemia. As in our patient, patients with HHCS apply to many outpatient clinics and have difficulty in diagnosis. For this reason, we prepared our case to raise awareness.

Keywords: Cataract, hyperferritinemia, iron

INTRODUCTION

Hyperferritinemia-cataract syndrome is a disease characterized by ferritin (hyperferritinemia) in the blood, a protein that causes excessive accumulation of iron in the tissues of the body. The accumulation of this protein begins in the early hours of life and causes the lenses to become cloudy (cataracts). In affected individuals, as in the general population, it usually develops in infancy and after age 60. Cataracts that are not surgically removed cause progressive darkening and blurred vision because blurred lenses reduce and distort the incoming light. Our aim in this case is to increase the clinical awareness Hereditary Hyperferritinemia Cataract Syndrome (HHCS) as a cause of hyperferritinemia in the presence of iron deficiency anemia and in the absence of iron accumulation and to form a diagnosis scheme as possible.

CASE

A 39-year-old female without a known chronic disease has been suffering from joint pain, fever and fatigue since 1995. In 2004 she underwent cataract surgery. The patient was later diagnosed with iron deficiency anemia (low serum iron and low transferrin saturation) and received iron replacement. Due to ongoing complaints, the patient was treated for 2 years with an initial diagnosis fibromyalgia (there is no documented record of this issue). Later, in rheumatology outpatient clinics, it was determined that there was no rheumatologic pathology, patient's high serum ferritin levels was associated with iron replacement therapy (Table).

In follow-up with persistent high serum ferritin levels the patient was directed to our department of hematology. It was revealed that the patient had hyperferritinemia before iron replacement therapy (first documented value: 1469 ng/ml). The patient evaluated for hemochromatosis, but there was no family history and transferrin saturation was low. The patient had a family history of early-onset cataracts with her mother, two of her aunts, uncle and with her children (both daughter and son) all requiring cataract surgery at an early age. Molecular genetic analysis showed patient is heterozygous for the FTL: c-160G>A substitution (also known as + 40A>G). Also molecular genetic analysis of patient's children (both son and daughter) and mother (which was living in Norway) were consistent with hereditary hyperferritinemia cataract syndrome (Figure). The patient's 26-year-old daughter had iron deficiency anemia and was treated with iron.

DISCUSSION

HHCS is an autosomal dominant inherited rare genetic disease. HHCS is an example of deregulation of the iron regulatory element (IRE)- iron regulatory protein (IRP) system. Heterozygous mutations of the L-ferritin mRNA in IRE make it unresponsive to IRP binding and translation suppression.

Table. Laboratory values of the patient and daughter over time.

DATE (PATIENT)	Ferritin ng/mL	Hgb g/dL	RCB 10^6/mL	Hct** %	Iron mg/dL	UIBC* mg/dL
06/2010	1469					
08/2012		10	4.59	31		
02/2013	1585					
03/2013	1438	10.3	4.93	35		
09/2013	1545	8.9	4.57	30	14	458
06/2014	>2000	10.2	4.7	31	15	441
07/2014	1607	10.8	4.96	35	16	453
12/2014	>2000	9.7	4.6	30	17	385
09/2015	1516	7.4	4.20	27	12	448
04/2016	2296		4.7	40.3	64	375
DATE (DAUGTER)	**Ferritin ng/mL**	**Hgb g/dL**	**RCB 10^6/mL**	**Hct** %**	**Iron mg/dL**	**UIBC* mg/dL**
09/2012	1221	11.8	4.45	35.8	19	404
08/2013		12.6	4.69	38.4	104	469
05/2014	>2000	12.0	4.5	38.2	56	449
09/2015	1500	12.6	4.54	39.5	46	410
DATE (SON)	**Ferritin ng/mL**	**Hgb g/dL**	**RCB 10^6/mL**	**Hct** %**	**Iron mg/dL**	**UIBC* mg/dL**
07/2014	1632	15.2	4.9	43.3	91	333
09/2015	1366	14.8	4.89	44.1	116	344

*UIBC: Unsaturated iron binding capacity **Hematocrit

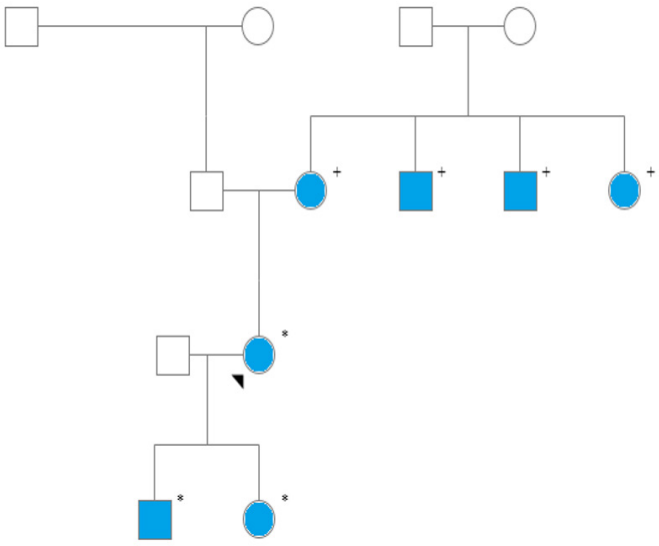

Figure. Family pedigree (plus: history of cataract , asterisk: genetically proven of HHCS)

Protein synthesis is continuous and iron independent. Serum ferritin levels are high, but total body iron and serum hepcidin levels are normal. In HHCS, ferritin accumulates in all cells in the body.[1] However, it causes cataracts by becoming toxic through forming L-ferritin crystal deposit formations only in the lens. Investigations of lens deposits with electronic microscopy revealed that lens deposits were crystals of L- ferritin. HHCS is usually not associated with anemia, and iron deficiency is usually not associated with an elevated serum ferritin. Distinguishing hyperferritinemia in HHCS with no iron overload from hyperferritinemia in hemochromatosis with iron overload is important.[2] In our case, the patient and her daughter had intermittent iron replacement therapy. HHCS may occur in patients with iron deficiency anemia without developed symptomatic cataract. So in this type of patients receiving iron replacement therapy could aggrevate the process of cataract formation. There is no specific treatment for HHCS. Cataracts are the only known complication of the disorder. Individuals are treated with corrective glasses, contact lenses and, if vision is impaired to the point of interference with daily activities, then cataract surgery is performed. Therapy involving the regular removal of blood via a vein (known as a phlebotomy) is a common therapy for disorders associated with excess iron in the blood, but is not recommended as a therapy for HHCS.[3]

CONCLUSION

HHCS should be considered in patients with family history, cataract, and hyperferritinemia, and genetic tests should be used for definitive diagnosis.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Pancreatic metastasis of renal cell carcinoma: a case report

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ABSTRACT

Pancreatic metastases constitute a mere 2% of all pancreatic cancers and are considered to be uncommon. Metastases to the pancreas arise from various organ systems in the body, with a higher incidence observed from the lung, breast, kidney, and gastrointestinal tract. It may manifest years following the therapy of the underlying tumor. At the time of initial diagnosis, symptoms such as stomach discomfort, weight loss, and jaundice are evident. However, they can also be identified using radiologic imaging even in the absence of any noticeable symptoms. This article describes a case where renal cell carcinoma (RCC) spread to the pancreas 16 years after the first therapy. The metastasis was discovered incidentally using endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB).

Keywords: Biopsy, EUS, metastasis, RCC, pancreas

INTRODUCTION

The majority (95%) of pancreatic malignancies are classified as exocrine pancreatic tumors. Most exocrine pancreatic malignancies arise from the epithelium of the duct, and ductal adenocarcinoma is recognized as pancreatic cancer.[1] Pancreatic metastasis is an infrequent occurrence. Pancreatic metastases account for 2% of all pancreatic cancers.[2] The primary tumors typically include lung, breast, renal cell, malignant melanoma, gastrointestinal, prostate, and less commonly osteosarcoma, leiomyosarcoma, chondrosarcoma, and Merkel cell carcinoma.[3] We are discussing an individual who underwent a surgical procedure (left nephrectomy) to treat renal cell carcinoma (RCC). After a period of 16 years, endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) was performed and it revealed the presence of renal cell carcinoma (RCC) metastases in the pancreas.

CASE

A 61-year-old male patient was referred to our hospital for an EUS-FNAB of a mass in the tail of the pancreas. The lump was discovered incidentally during exams conducted at another medical facility. An abdominal computed tomography (CT) scan conducted at an external facility detected a highly vascular, 3.5 cm-sized mass in the pancreatic tail during the arterial phase. The physical examination yielded no notable findings save for the presence of left hemiplegia. The test results indicated a platelet count of 112.000 per microliter (µL). Standard biochemical tests, measurements of blood clotting, cancer antigen (CA 19-9), and carcinoembryonic antigen (CEA) levels were within normal range. The patient's medical background comprises a complete surgical removal of the left kidney as a result of RCC two decades ago, a surgical removal of a lobe of the left lung due to the spread of cancer, left-sided paralysis caused by a blockage of blood flow to the brain three years ago, and a diagnosis of diabetes mellitus. The patient was admitted to our clinic. The linear endoscopic ultrasound (EUS) examination detected a 3.5-cm-diameter mass in the tail of the pancreas. The mass appeared to be heterogeneous and had thin vascular structures surrounding the inferior vena cava (VCI). It was observed that the mass extended into the VCI, resembling either a mass or a tumor thrombus, as shown in the figure. Two EUS-FNAB procedures were conducted using a 22G needle. The biopsy findings indicated the presence of metastatic renal cell carcinoma. The patient's Memorial Sloan-Kettering Cancer Center score for metastatic RCC was 1, placing them in the intermediate risk group with a median follow-up period of 10 months. The patient was released with a scheduled appointment for medical oncology follow-up.

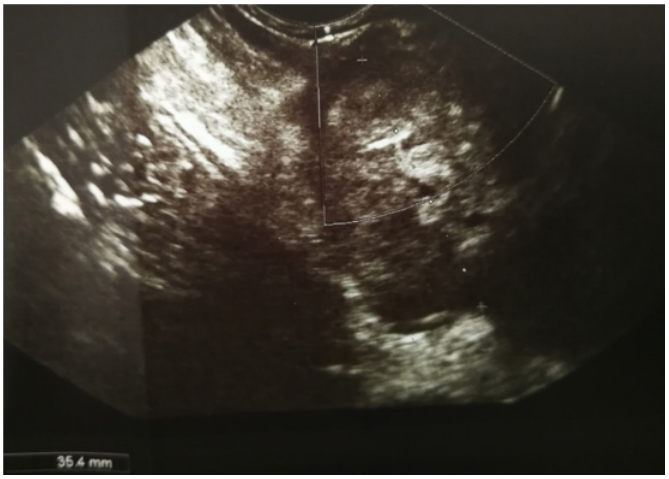

Figure. RCC metastasis in the tail section of the pancreas. EUS image of the patient

DISCUSSION

Pancreatic metastases are uncommon, comprising about 2% of all pancreatic cancers, while autopsy collections have reported rates as high as 12%.[2] The most prevalent types of cancer that spread to the pancreas are lung, breast, renal cell carcinoma, malignant melanoma, gastrointestinal cancers (including stomach, colon, rectum, and duodenum), prostate, and lymphoma. Osteosarcoma, leiomyosarcoma, and chondrosarcoma have lower reported rates of metastasis to the pancreas.[3]

Metastasis to the pancreas can either be without symptoms or result in symptoms such as stomach pain, loss of weight, nausea, jaundice, gastrointestinal bleeding, and blockage.[4] Pancreatic metastases can manifest in three distinct forms: 1) a solitary localized mass (50-73%), 2) diffuse enlargement of the pancreas (15-44%), and 3) numerous nodules in the pancreas (5-10%).

The spread of renal cell carcinoma (RCC) to the pancreas can occur several years following the surgical removal of the kidney. According to reports, 11% of patients who had a nephrectomy for renal cell carcinoma (RCC) experienced pancreatic metastasis within 10 years. Additionally, one patient acquired pancreatic metastasis after a period of 32 years.[5] Colorectal, stomach, and lung metastases appear to have reduced blood supply on arterial phase imaging in CT scans, while neuroendocrine tumors, hepatocellular carcinoma (HCC), and renal cell carcinoma (RCC) metastases appear to have increased blood supply2. When a hypervascular abnormality is identified in the pancreas on CT scan, it is important to investigate vascular abnormalities (such as splenic artery aneurysm) and the presence of an additional spleen within the pancreas as potential causes, in addition to the possibility of malignancies.[6] To get a histopathologic diagnosis, either an EUS-FNAB or a percutaneous biopsy can be performed.

No renal cell carcinoma (RCC), other primary malignancies, accessory spleen, or aneurysm were seen in our patient's other kidney based on imaging. The presence of RCC metastases was established using EUS-FNAB.

CONCLUSION

When determining the nature of a pancreatic tumor, it is crucial to search for synchronous or metachronous metastases. This is particularly crucial in those with a history of cancer, and appropriate testing should be scheduled accordingly. For these patients, it is advisable to consider EUS-FNAB due to its reliability and excellent diagnostic accuracy.

ETHICAL DECLARATIONS

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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