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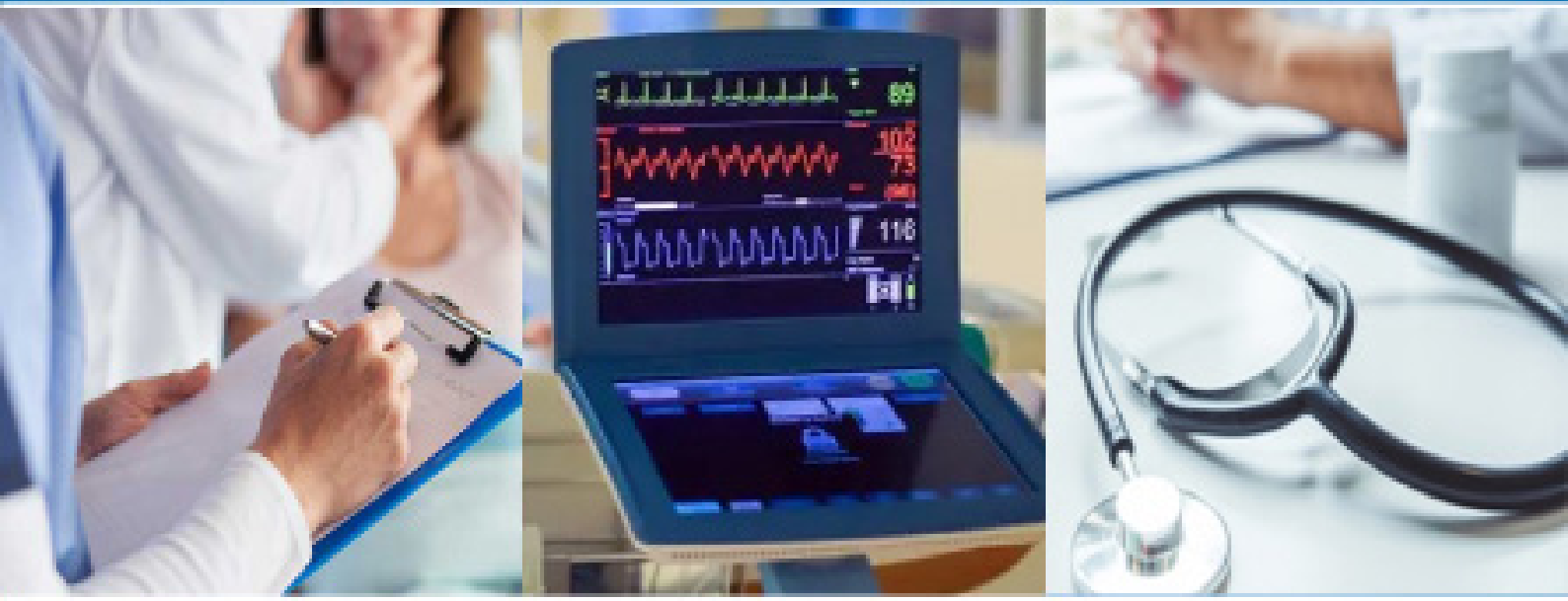

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Original Article

C-reactive protein, fibrinogen, prothrombin time and international normalized ratio levels as indicators of chronic inflammation in patients with metabolic syndrome

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ABSTRACT

Aims: Although it has been stated in studies conducted in patients with metabolic syndrome (MetS) that elevated serum fibrinogen and C-reactive protein (CRP) may be due to chronic inflammation, sufficient studies have not been conducted on International normalized ratio (INR) and prothrombin time (PT). The aim of this study is to examine the fibrinogen, INR and PT levels of patients with MetS and to investigate the relationship between these parameters and MetS components.

Methods: A total of 56 patients, 19 males and 37 females were included in our study who applied to the Internal Medicine outpatient clinic of Ondokuz Mayıs University Faculty of Medicine and met the MetS diagnostic criteria. The control group consists of a total of 64 people, 35 men and 29 women, who have at least one of the MetS criteria and do not have a chronic disease. Fasting blood glucose, total cholesterol (total-C), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine, thyroid stimulating hormone (TSH), PT, INR and fibrinogen levels were examined from the available samples. Data were compared between healthy and patient groups.

Results: As a result of our study, it was determined that the CRP level was significantly higher in the patient group ($p<0.01$). The average fibrinogen level was calculated as 3.56 g/L in the patient group and 2.95 g/L in the control group, and a significant difference was detected when the two groups were compared ($p<0.001$). The average PT value was 13.1 in the patient group and 12.04 in the control group and a significant difference was detected between both groups ($p<0.001$). The average INR level was 1.14 in the patient group and 1.04 in the control group and a significant difference was detected between both groups ($p<0.001$).

Conclusion: MetS is associated with high CRP. In patients with MetS, PT, INR and fibrinogen levels are also high. In the follow-up and treatment of patients with MetS, the presence of chronic inflammation and factors affecting the coagulation system should be taken into consideration.

Keywords: Prothrombin time, international normalized ratio, fibrinojen, metabolic syndrome

INTRODUCTION

Metabolic syndrome (MetS), also known as syndrome X, insulin resistance, polymetabolic syndrome, is defined by the World Health Organization (WHO) as a multisystem disease characterized by abdominal obesity, insulin resistance, hypertension and hyperlipidemia.[1] The pathophysiology of MetS involves many complex mechanisms that have not yet been fully elucidated. The pathogenesis of MetS involves multiple genetic and environmental factors, including insulin resistance and chronic low-grade inflammation.[2] IL-6 production increases with increasing body fat and insulin resistance. Increased IL-6 affects the liver, bone marrow, and endothelium, leading to increased production of acute phase reactants, including C-reactive protein (CRP). Various studies have shown a correlation between high CRP levels and the development of MetS, diabetes and cardiovascular disease.[3-5]

Endothelial dysfunction is a complex pathological condition associated with increased activity of coagulation factors, hyperactivity of platelets and decreased fibrinolysis.[6] In patients with MetS, there is increased synthesis of fibrinogen and plasminogen activator inhibitor 1 (PAI-1) in the liver as a result of hyperinsulinemia and increased IL-6 levels. Factor VII, IX and X levels also increase which occur as a result of activation of endothelial cells. These changes in hemostatic balance contribute to the susceptibility to thrombosis in MetS

and constitute the atherothrombotic process underlying acute coronary or cerebrovascular events.[2,7]

In light of all this information, while CRP and serum fibrinogen levels due to chronic inflammation are often high in individuals with MetS, very few studies have been conducted on International normalized ratio (INR) and prothrombin time (PT). The aim of this study is to evaluate fibrinogen, INR and PT levels of patients with MetS and to investigate the relationship between these parameters and MetS components. We also believe that we will contribute to future studies on prophylactic anticoagulation therapy to prevent thrombosis in patients with MetS.

METHODS

A total of 56 patients between the ages of 18 and 65, who applied to the Department of Internal Medicine at Ondokuz Mayıs University Faculty of Medicine between May 2012 and September 2013 and were diagnosed with MetS according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria, were included in our study. Approval for the study was received from Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 26.04.2012, Desicion no: 2012/8). Informed written consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki. The control group consists of 64 healthy individuals with similar demoFigureic characteristics to the patient group in terms of age and ethnicity. Patients with a history of renal failure, liver disease, hypothyroidism, acute infection, malignancy, pregnancy, autoimmune disease and patients receiving hormone replacement therapy were excluded from the study. DemoFigureic information of the participants, such as age, gender, height, weight, body-mass index (BMI), waist circumference, education level and occupation, were recorded. Venous blood samples were collected into biochemistry tubes containing anticoagulant and without anticoagulant additives after a 12-hour fast. After the samples were centrifuged for one hour, the serum was separated and placed in the -80°C deep freezer on the same day. Data were created by looking at fasting blood glucose, total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine, thyroid stimulating hormone (TSH), PT, INR and fibrinogen levels from the available samples. Fasting blood glucose, total cholesterol, TG, HDL and uric acid were studied in the biochemistry laboratory using Roche Diagnostics kits on a Hitachi Cobas 8000 autoanalyzer.

NCEP-ATP III components include the presence of central obesity (waist circumference >102 cm in men >88 cm in women), hypertriglyceridemia (TG ≥150 mg/dL or specific drug use), low HDL level (men<40 mg/dl, women <50 mg/dL), high fasting blood glucose (≥110 mg/dL) and high arterial blood pressure (≥130/85 mmHg). MetS is diagnosed if three or more of these components are present.

Statistical Analysis

Statistical analyzes of the data were performed using the SPSS 15 package program. Numerical data are shown as±standard deviation. Mann-Whitney U and Chi-Square tests were used to compare patient and control groups, and Spearman and Pearson correlation analyzes were used to examine the relationships between the data. Non-parametric data were interpreted with Kruskal-Wallis analysis. All analyzes were performed with a 95% confidence interval. A value of $p<0.05$ was considered as statistically significant.

RESULTS

There were 19 men and 37 women in the patient group, and 35 men and 29 women in the control group. A significant difference was detected between genders when both groups were compared. The weight, waist circumference, systolic blood pressure, diastolic blood pressure, mean blood pressure, and fasting blood glucose of the patient group were found to be statistically significantly higher than the control group (Table 1). Considering the upper limit value for CRP value as 3.3 mg/dL, it was determined that 39 people (69.6%) in the patient group were higher than the limit value and 17 people (30.4%) were lower than the limit value. In the control group, 49 people (76.4%) were found to be lower than the limit value and 15 people (23.6%) were found to be higher. The number of patients with high CRP values was found to be statistically significantly higher in the patient group ($p<0.001$) (Table 2).

Table 1. Comparison of clinical and laboratory data of the patient and control groups

	Patient group, mean±SD	Control group, mean±SD	p value
Height (cm)	160.95±10.09	167.2±9.18	<0.001
Weight (kg)	91.6±16.61	74.7±13.73	<0.001
Waist circumference (cm)	114.08±14.32	88.8±11.83	<0.001
BMI (kg/m²)	35.3±6.37	27.09±4.51	<0.001
Systolic blood pressure (mmHg)	127.14±17.5	109.69±8.91	<0.001
Diastolic blood pressure (mmHg)	76.07±9.08	70.16±7.01	<0.001
Mean blood pressure (mmHg)	93.02±10.8	83.2±6.52	<0.001
Fasting blood glucose (mg/dL)	189.34±69.64	88.6±18.95	<0.001
Triglyceride (mg/dL)	246.07±120.22	198.6±115.83	0.03
HDL (mg/dL)	31.14±11.12	47.5±14.42	<0.001
Fibrinogen	3.56±1.01	2,95 ± 0.77	<0.001
PT	13.16±2.70	12.04±1.10	<0.001
INR	1.14±0.25	1.04±0.01	<0.001

SD: Standard deviation, BMI: Body-mass index, HDL: High density lipoprotein, PT: Prothrombin time, INR: International normalized ratio

Table 2. Comparison of patient numbers in the patient and control group in terms of c-reactive protein

	Patient group n (%)	Control group n (%)	p value
CRP>3.3	39 (69.6)	15 (23.4)	<0.001
CRP<3.3	17 (30.3)	49 (76.5)	

*The CRP cut off value of our hospital is 3.3, CRP: C-reactive protein

The distribution of MetS components in the patient and control groups is shown in Figure 1.

In the patient group, the patient distribution was examined according to the number of criteria and the average fibrinogen, PT and INR levels were calculated (Figure 2).

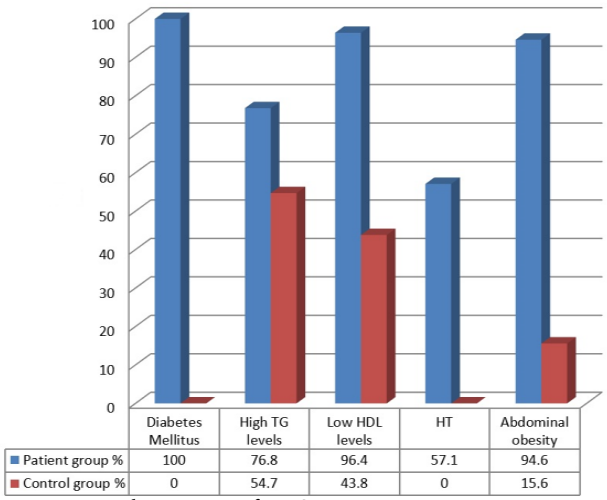

Figure 1. Distribution rates of MetS components

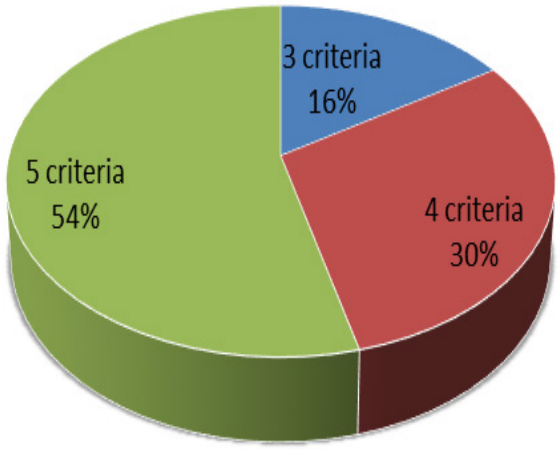

Figure 2. Distribution of patients according to metabolic syndrome criteria numbers

While fibrinogen, PT and INR levels in the female patient group were significantly higher than those in the control group, no significant difference was detected between the patient and control groups in men (Table 3).

Table 3. Comparison of PT, INR and fibrinogen levels by gender

	Female			Male		
	MetS (+)	MetS (-)	p value	MetS (+)	MetS (-)	p value
PT	13.49±2.9	11.98±0.87	p<0.01	12.49±2.16	12.10±1.28	>0.05
INR	3.57±0.82	1.03±0.01	p<0.01	3.32±0.74	2.81±0.51	>0.05
Fibrinogen	3.52±0.13	2.95±0.08	p<0.01	3.32±0.7	2.81±0.08	<0.05

PT: Prothrombin time, INR: International normalized ratio

No statistically significant difference was detected in the change in PT, INR and fibrinogen levels as the number of MetS components increased (p>0.05) (Table 4).

Table 4. Change in PT, INR and fibrinogen levels with metabolic syndrome criteria number

	3 criteria together	4 criteria together	5 criteria together	p value
PT	12.58±1.00	13.83±0.77	12.94 ±0.43	
INR	1.09±0.09	1.20±0.07	1.12±0.03	>0.05
Fibrinogen	3.51±0.29	3.73±0.21	3.33±0.12	

PT: Prothrombin time, INR: International normalized ratio

A positive correlation was found between waist circumference and PT, INR and Fibrinogen in the MetS group. Strong positive correlations were observed between fasting blood glucose and PT, INR and fibrinogen.While mean blood pressure and TG levels showed a positive correlation with PT and INR levels, these results were not statistically significant.A statistically non-significant negative correlation was observed in HDL levels with PT, INR and fibrinogen (Table 5).

DISCUSSION

MetS is a component of pathological conditions associated with metabolic, proinflammatory and prothrombotic states.[8] This syndrome involves increased levels of coagulation factors (tissue factor, factor VII and fibrinogen) as well as inhibition of the fibrinolytic pathway (increase in PAI-1 and decrease in tissue plasminogen activator activity). It also has characteristics of a hypercoagulation state. The simultaneous presence of endothelial dysfunction and dyslipidemia triggers platelet aggregation, thus further increasing the risk of thrombotic events in both the arterial and venous systems.[9]

MetS increases with age. In a meta-analysis study, the average age of MetS patients was calculated as 41 years.[10] In the study of Gündoğan et al.,[11] the average age was reported as 47 years, and the frequency of MetS increased as age increased. In our study, the average age of MetS patients was found to be 52.9±12.08 years.

The frequency of MetS is increasing all over the world. According to the National Health and Nutrition Research Survey (NHANES) in the USA, it is known that 35% of adults and 50% of the population over the age of 60 are diagnosed with MetS (30.3% in men and 35.6% in women). While the European Met prevalence is 41% in men and 38% in women, in the Middle East it has been reported as 20.7-37.2% in men

Table 5. Relationship of metabolic syndrome components with PT, INR and fibrinogen

	PT		INR		Fibrinogen	
	Sperman correlation coefficient	p	Sperman correlation coefficient	p	Sperman correlation coefficient	p
Waist circumference (cm)	0.251**	0.007	0.250**	0.007	0.195*	0.036*
Blood pressure (mm/Hg)	0.070	0.456	0.062	0.510	0.220	0.018
FBG (mg/dL)	0.279**	0.002	0.283**	0.002	0.239**	0.010
HDL (mg/dL)	-0.049	0.603	-0.048	0.609	-0.113	0.229
TG (mg/dL)	0.059	0.530	0.077	0.413	0.045	0.633

**Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed), FBG: Fasting blood sugar, HDL: High density lipoprotein, TG: Triglyceride

and 32.1-42.7% in women.[12] According to the TEKHARF 2000 follow-up database in Turkey, it was reported as 27% in men and 38.6% in women, while according to the METSAR research conducted in 2004, it was found to be 28% in men, 39.6% in women and 33.9% in total. The prevalence of MetS increased with age in men, and while it was found to be 10.7% in those aged 20-29, it increased to 49% in people over 70 years of age. The prevalence in women also increased with age, from 9.6% in those aged 20-29 to 74.6% in those aged 60-69. When we evaluated the PURE data in 2009, it was observed that the prevalence of MetS was between 36.7% and 43.6%.[13-15] In our study, 33.9% of 56 patients were male and 66.1% were female.

When the components of MetS were evaluated, it was reported that abdominal obesity and high blood pressure were the most common metabolic findings in the METSAR study, abdominal obesity and low HDL in Tabatabaie et al.'s[16] study, and low HDL in Sharifi's study.[17] In the study of Gündoğan et al,[11] the most common component of MetS in our country was found to be hypertension. In our study, the distribution rates of MetS components were found to be high fasting blood sugar 100%, hypertension 57.1%, hypertriglyceridemia 76.8%, low HDL 96.4%, and abdominal obesity 94.6%.

Various pathogenic pathways that contribute to the development of MetS lead to the increase in various inflammatory markers such as IL-6, CRP and TNF-α seen in patients with MetS.[3] In the study of Weisberg et al,[18] it was shown that the increase in IL-6 level increased with insulin resistance and obesity.[19] In the study of Malik et al,[20] they found that the CRP level increased in patients with MetS and diabetes, and that this increase was more pronounced in people with cardiovascular disease. In our study, CRP elevation was found to be statistically significantly higher in the patient group.

MetS has a complex pathophysiology associated with an increased risk of both atherothrombotic cardiovascular events and venous thromboembolism. In addition to affecting the thrombogenicity of circulating blood as a result of the inflammatory state accompanying MetS, dyslipidemia and fat accumulation in the liver, a procoagulant and hypofibrinolytic state has been described.[21] In MetS, high IL-6 levels also increase fibrinogen levels and causes a prothrombotic state.[2] High fibrinogen levels have been reported in many MetS studies. In the TEKHARF study, which started in 1998 and included 2516 participants, the mean plasma fibrinogen level was found to be 3.12±1.11 g/L. It was also reported in the study that fibrinogen levels significantly increase with age in both genders.[13] In the study of Imperatore et al.,[22] fibrinogen values were associated with BMI, waist-hip ratio, systolic and diastolic blood pressure, plasma total cholesterol, LDL cholesterol, triglycerides, insulin and HDL. Khunger et al.[23] reported fibrinogen as the most sensitive coagulation parameter in MetS. In our study, fibrinogen levels increased significantly in the MetS group compared to the healthy group. Additionally, a significant positive correlation was found between fasting blood sugar and waist circumference.

PT, one of the indicators of the extrinsic coagulation system in MetS, and activated partial thromboplastin time (APTT), which is the intrinsic coagulation system, have been reported to be significantly low in many studies.[23] Injury to endothelial cells has been held responsible for this prothrombotic state by causing an increase in the levels of factors VII, IX and X, prothrombin and PAI-1.[19] The fact that PT and INR are significantly higher in MetS suggests that it may be in a hypocoagulant state rather than a procoagulant state. In a study conducted by Habib et al.[24] in patients with alcoholic hepatitis, INR and PT levels were found to be higher in the patient group with MetS than in the patient group without MetS. Similar to this study, PT and INR values were found to be significantly higher in the patient group in our study.

Limitations

Our study has some limitations. These limitations are the small number of patients and the lack of more parameters indicating clotting factors. Although our study has a low sample size, it has several important implications.

CONCLUSION

In our study, high fibrinogen values indicate the presence of hypercoagulopathy in patients with MetS, while high PT and INR values seem to indicate hypocoagulopathy. There are no current guidelines regarding the administration of prophylactic anticoagulation in MetS.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Ondokus Mayıs University Clinical Researches Ethics Committee (Date: 26.04.2012, Desicion no: 2012/8).

Informed Consent

The patient 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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Original Article

Evaluation of clinical data of patients with pancreas cancer

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ABSTRACT

Aims: The main purpose of the study is to determine the prognostic factors by retrospectively evaluating the clinical data of patients with pancreatic cancer.

Methods: The patients diagnosed with pancreatic adenocarcinoma (132) were analyzed retrospectively. Age, gender, blood group, tumour localization, tumour stage (TNM classification), postoperative chemotherapy, postoperative radiotherapy status, progression-free survival and survival time as prognostic factors were evaluated. Women and men, tumours located in the head region versus those located in the trunk and tail regions, those who received chemotherapy and/or radiotherapy versus those who did not, those who were in stage 2 The patients with stage 3, stage 4, "A" blood group, "B" blood group and "O" blood group were compared with each other and subgroup analysis was performed.

Results: In our study, 59.8% were male and 40.2% were female of the cases. According to TNM staging, 34 (26%) of our cases were found as stage 2.27 (20%) as stage 3, 71 (54%) as stage 4. Progression-free survival and survival times of patients with stage 2 cancer were found to be significantly longer when compared to patients with stage 3 and 4 ($p<0.01$). Among stage 2 and 3 patients, 45 (38.6%) patients, 26 patients with stage 4 (19.6%) received chemotherapy, and 9 patients (6.81%) received chemotherapy and radiotherapy concurrently. The tumour was most common in the head of the pancreas [93/132 (70.5%)]. Progression-free survival and survival of tumour localization, receiving chemotherapy, and tumour stage was found to affect the duration of the study statistically significantly ($p<0.001$).

Conclusion: It was determined that chemotherapy and tumour stage affected progression-free survival and survival times with statistical significance. Ca 19-9 and CEA level measurement values can be used in the follow-up of patients with pancreatic cancer. EUS is useful at pancreas cancer diagnosis and staging.

Keywords: Pancreatic cancer, prognostic factors, Ca 19-9, CEA, EUS

INTRODUCTION

Cancer is the second most common cause of death after cardiovascular diseases with a rate of 22% both in the world and in our country.[1] Pancreatic cancer is the 9th most common cancer in our country and its annual incidence is; It has been found to be around 4.5/100,000.[2] Pancreatic adenocarcinoma is among the top 10 causes of cancer-related deaths in developed countries.[3,4] Among all gastrointestinal cancers, pancreatic cancer has attracted attention with its increasing frequency in recent years.[5] In most countries, its incidence has increased dramatically as living conditions have become more westernised. The highest incidence rate occurs in the 7th and 8th decades of life, and the diagnosis is made at an average age of 60-65 years.[6]

Adenocarcinoma is the most common histology, accounting for 95% of cases. It is seen 50-100% more frequently in men than in women. Current imaging techniques have shown that; despite advances in surgery, chemotherapy, and radiotherapy, the life expectancy of patients with pancreatic cancer has increased slightly.[7] Pancreatic cancer; it is one of the few cancer types with 100% mortality.[7,8] It has the shortest life expectancy among all cancer types.[9] Pancreatic cancer, which is the gastrointestinal system tumour with the worst prognosis with an incidence close to its mortality, has the worst prognosis among all solid tumours.[10]

Pancreatic cancer quickly results in death. Compared with all cancer types, the 5-year survival rate is 10% in patients diagnosed with pancreatic cancer at all stages.[11] When the tumour is detected only when it has invaded the pancreas, the 5-year survival is only 25-30% after surgery.[10] Many factors thought to be effective on the prognosis in pancreatic cancer have been the subject of research. Gender, age, blood group, body mass index, tumour localization, histological grade, stage, metastatic lymph node, tumour markers (CEA, Ca 19-9), preoperative haemoglobin and albumin

level, chemotherapy, radiotherapy administration, resected pancreatic cancer investigated as prognostic factors in patients In the treatment of pancreatic cancer, one or more of the three treatment modalities, surgery, radiotherapy and chemotherapy, can be used in combination. Only about 15-20% of newly diagnosed pancreatic cancers is resectable and is added to adjuvant chemotherapeutic therapy.[12] The stage of the disease should be considered in the treatment approach. Surgery is the only potential curative treatment for pancreatic cancer. In patients with distant organ metastases and locoregional irresectable tumours, the primary treatment option is chemotherapy, and radiotherapy can be added to chemotherapy.[13]

In this retrospective study, gender, age, occupation, blood type, symptoms and clinical findings at the time of admission of 132 patients diagnosed with pancreatic cancer and admitted to Zonguldak Karaelmas (Bülent Ecevit) University Faculty of Medicine Application and Research Hospital Internal Diseases Medical Oncology Clinic between February 2000 and March 2011, smoking and alcohol use, systemic diseases, family history of cancer, tumour localization, histological grade and stage, metastatic lymph node, whether surgery was performed, chemotherapy and radiotherapy were investigated. In this study, it was aimed to evaluate the effects of these prognostic factors on survival times in detail.

METHODS

Group design

The study group consisted of 132 patients who applied to Zonguldak Karaelmas (Bülent Ecevit) University Medical Faculty Application and Research Hospital Medical Oncology Outpatient Clinic between February 2000 and March 2011 and were diagnosed with pancreatic adenocarcinoma in our hospital or another medical center. Information about the patients was obtained by retrospectively examining the patient files. Information about patients who did not come for control for a long time was updated as of March 2011 by calling their homes. Ethics committee approval for the study was received from Zonguldak Karaelmas (Bülent Ecevit) University Faculty of Medicine Hospital Ethics Committee (Date: 08.03.2011, Decision No: 2011/02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki

Patients' age which cancer was diagnosed, gender, occupation, complaints on admission, clinics at the time of admission, blood types, smoking and alcohol use, family history of cancer, whether or not they were operated on, the localization of the tumour, its stage, treatment modalities and chemotherapy protocols applied to the patients, local The site of recurrence and/or metastasis, the treatment modalities of the patients with metastasis, the last date of admission to our polyclinic, the latest updated status, the date of death of the patients who died were recorded, and the prognostic factors affecting the survival time: age, gender, blood type, tumour localization, tumour location. Stage (TNM classification), postoperative chemotherapy, and postoperative radiotherapy status were investigated.

General follow-up period; time from diagnosis to end of study, overall survival; The time from the date of diagnosis to the date of death or the update of patient information for surviving patients, and progression-free survival were expressed as the time from the date of diagnosis to the development of local recurrence and/or metastasis.

Statistical Analysis

SPSS for Windows 18.0 package program was used in the analysis of the study. In the study, variables with categorical values are given with numbers and percentages, and measurement variables with continuous values are given with mean, median, standard deviation, minimum and maximum values. The conformity of the measurement variables to the normal distribution was analysed with the Shapiro Wilks test. Kruskal Wallis analysis of variance was used to compare the variables in 3 groups, and the Mann Whitney U test was used for comparisons of 2 groups. Wilcoxon test was used for in-group comparisons of measurement variables according to the onset time. Correlation analysis was performed for the significance of the change between the measurement variables and the significance was interpreted with the Spearman correlation coefficient. Chi-square test was used for intergroup comparisons of categorical variables. Comparisons with a p value below 0.05 were considered significant in the analyses in the study.

RESULTS

The distribution of 132 cases with pancreatic adenocarcinoma, taken as the study group, by gender is given in Table 1. There were 9 cases under the age of 45, 39 cases between the ages of 45-60, and 84 cases over the age of 60. The mean age of our cases was 65 (±12). The male/female ratio was found to be 1.49.

A palpable mass was found on physical examination in 18 (13.6%) of the cases. When pancreatic adenocarcinomas were evaluated according to their localizations, 70.5% were located on the head, 19% on the trunk, and 14% on the tail. Accordingly, it was determined that the tumour was most frequently encountered in the head. When the cases were analysed according to their smoking characteristics, it was found that 59 (44.7%) of 132 cases were smokers, and 73 (55.3%) were non-smokers. The number of pack-years in smokers ranged from 10 to 150, with an average of 32.2±22.3 pack-years. When the cases were analysed according to their alcohol use characteristics, it was found that 10 (7.6%) of 132 cases used alcohol, and 122 (92.4%) did not use alcohol. It was not possible to reach the amount of alcohol consumed in patients who used alcohol due to insufficient data.

When the cases were considered in terms of comorbid systemic diseases, the most common comorbid systemic disease was hypertension, and diabetes mellitus was the second most common comorbid disease. When the family history of cancer was investigated, a family history of cancer was found in 9 patients, but not in 123 patients. While cancer was found in one person in the family in 5 of the patients with a family history of cancer, cancer was found in 2 people in the families of 4 people. Diagnostic laparoscopy and/or laparotomy were performed in 36 (27.5%) cases. When the data of the regions where metastases were detected for the first time were analysed, it was determined that the tumours most frequently made their first metastases to the liver. The second most common metastasis was to vascular structures.

Table 1. The distribution of 132 cases with pancreatic adenocarcinoma, taken as the study group, by gender

	Patient number (n)	Percentage %
Gender		
Male	53	40.2
Female	79	59.8
Total	132	100
Patient's complaint		
Abdominal pain	118	89.4
Jaundice	53	40.2
Vomiting	32	23.5
Weight loss	29	22
Back pain	6	4.5
Bloating	5	3.8
Itching	3	2.3
Blood group		
A Rh+	63	47.7
B Rh+	18	13.6
0 Rh+	39	29.5
AB Rh+	6	4.5
A Rh-	5	3.8
B Rh-	1	0.8
Total	132	100
Tumour localization		
Top	93	70.5
Body	25	19
Tail	14	10.5
Total	132	100
Smoking status		
Use	59	44.7
Not use	73	55.3
Total	132	100
Alcohol use status		
Use	10	7.6
Not use	112	92.4
Total	132	100
Concomitant disease		
No concomitant disease	42	31.8
Diabetes mellitus	14	10.6
Hypertension	38	28.8
Diabetes mellitus and hypertension	26	19.7
Malignancy	7	5.3
Chronic viral hepatitis	5	3.8
Total	132	100
Family history of cancer		
None	123	93.2
There is 1 person in the family	5	3.8
There are 2 people in the family	4	3
Total	132	100
Surgical procedure		
Whipple	45	34
Inoperable	41	31
Unresectable	10	7.5
First metastasis		
Unknown	2	1.5
Liver	84	63.6
Vascular	23	17.4
Peritoneum	14	10.6
Lung	9	6.8
Staging (American Joint Committee on Cancer, 2010)		
Stage 2 (T1-3 N0-1 M0)	34	26
Stage 3 (T4 any N M0)	27	20
Stage 4 (Any T any N M1)	71	54
Total	132	100

When the progression-free survival and overall survival times of our cases were evaluated according to gender; There was no statistically significant difference between male and female genders in terms of survival ($p>0.05$).

It was observed that 26 of our cases underwent diagnostic endosonography, and 11 of these 26 patients were Stage 2, 2 were Stage 3, and 14 were Stage 4. There were 5 patients who had CT angiography as well as EUS. Twenty of these cases had pathology results of the pancreas and surrounding tissue. It was observed that the diagnosis and stages of EUS and CT angiography and/or CT results of our cases were similar and the pathology results were consistent with these.

CASE

A 70-year-old male patient applied with the complaint of abdominal pain for 6 months. Abdominal pain was localized in the lower quadrants and was colic in character. Diabetes mellitus and hypertension was present. Abdominal CT scan of our case, which was taken due to abdominal pain, was reported as a mass of 5 cm in diameter in the pancreatic body (Figure 1A), suspicious hypodense areas with a diameter of 8 mm in segment 8 of the right lobe of the liver and 6 mm in diameter in segment 6 of the liver (Figure 1B). CA 19-9: 12000 ng/ml and CEA 120 ng/ml. Endosonography was performed to the patient with pancreatic body and a mass lesion of 5x5 cm heterogeneous echogenicity is seen and settled. İİAB was performed from the lesion with a 22 G needle (Figure 1C).

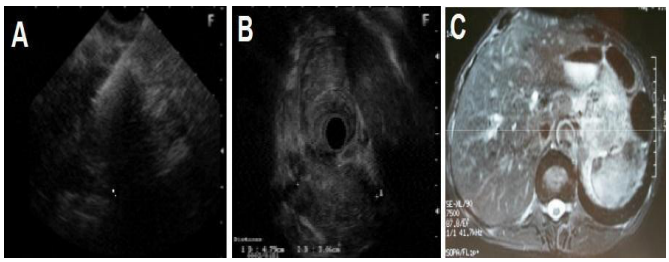

Figure 1. A-B: EUS Images C: Abdominal CT scan images

The result of the biopsy was reported as pancreatic adenocarcinoma (Figure 2A, B). The patient was offered an operation, but the patient refused. The patient was started on chemotherapy; after 4 cycles of chemotherapy, the patient died.

CA 19-9: 12000 ng/ml and CEA 120 ng/ml. Endosonography was performed on the patient with rheumatoid arthritis,

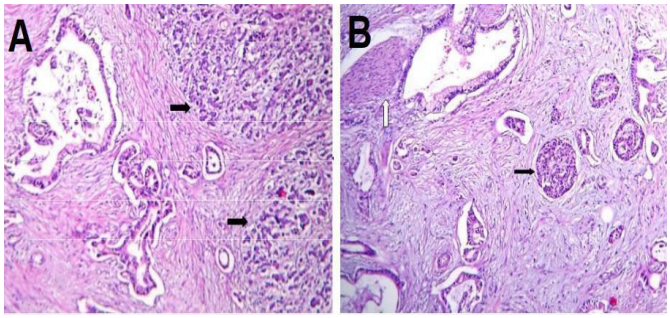

Figure 2. The results of the biopsy

and a mass lesion of 5x5 cm heterogeneous echogenicity located towards the tail part of the pancreatic body was seen. When the progression-free survival rates and overall survival times of our cases were evaluated according to tumour localization; a statistically significant difference was found in terms of survival times of those with tumour localization in the head compared to those located in the trunk and tail. (p<0.001). When progression-free survival and overall survival times were evaluated according to blood group, no statistically significant difference was found in terms of survival (p>0.05). When evaluated the progression-free survival and overall survival times by stage; A statistically significant difference was found in terms of survival time (p<0.01). Accordingly, progression-free and overall survival times of patients with stage 2 cancers were found to be significantly longer when compared to patients with other stages (Table 2).

It was observed that 45 of 132 cases were Stage 2 or 3 (34%) and received adjuvant chemotherapy, 26 (19.6%) were stage 4 and were evaluated as inoperable and received chemotherapy. It was observed that 9 of the cases received radiotherapy. Gemcitabine and cisplatin chemotherapy regimen were given to all those who accepted the treatment. When the progression-free survival and overall survival times were evaluated according to the chemotherapy receiving status of the cases; A statistically significant difference was found in terms of progression-free survival and overall survival in all stages (p<0.001). When the survival times of our cases were evaluated according to gender; There was no statistically significant difference between female and male genders in terms of survival time (p=0.08) (Table 2).

When the overall survival of our cases was evaluated according to whether they received radiotherapy or not, it was seen that 9 of them received radiotherapy and receiving radiotherapy did not increase the survival time statistically (Table 3).

When the diagnosis/progression/last visit moments of Ca 19-9 and CEA values of our cases were compared; It was observed that there was a statistically significant increase from the diagnosis towards the last visit (p=0.01) (Table 4).

Table 2. Survival times of patients

	Patient number (n)	Progression-free survival, median value (min-max)	Overall survival, median value (min-max)	p
Gender				
Male	79	3 months (1-40)	5 months (1-48)	
Female	53	4 months (1-40)	7.5 months (1-48)	>0.05
Total	132	4 months (1-40)	6.5 months (1-48)	
Tumour localization				
Top	93	4 months (1-40)	8 months (1-48)	
Body and tail	39	2 months (1-12)	3 months (1-20)	<0.001
Total	132	4 months (1-40)	6.5 months (1-48)	
Blood group				
A	67	3 months (1-22)	5 months (1-26)	
0	39	4 months (1-40)	5 months (1-48)	
B+AB	26	4.5 months (1-40)	6.5 months (1-48)	>0.05
Total	132	4 months (1-40)	6.5 months (1-48)	
Stage				
Stage 2	34 (%26)	12 months (4-40)	20 months (7-48)	
Stage 3	27 (%20)	5 months (1-12)	8 months (1-18)	<0.001
Stage 4	71 (%54)	2 months (1-9)	3 months (1-20)	
Total	132 (%100)	4 months (1-40)	6.5 months (1-48)	<0.001
Chemotherapy status				
Stage 2	34 (%26)	12 months (4-40)	20 months (7-48)	
Stage 3	27 (%20)	5 months (1-12)	8 months (1-18)	<0.001
Stage 4	71 (%54)	2 months (1-9)	3 months (1-20)	
Total	132 (%100)	4 months (1-40)	6.5 months (1-48)	<0.001
Stage 4				
Receive chemotherapy	26	3.5 months (1-9)	5.5 months (1-20)	
Did not receive chemotherapy	45	1 months (1-4)	2 months (1-6)	<0.001
Total	71	2.5 months (1-9)	3 months (1-20)	

Table 3. Survival times according to whether received radiotherapy or not

	Patient number (n)	Mean value±SD (min-max)	p
Radiotherapy			
Receive radiotherapy	9	9 months ±7 (0-20)	
Did not receive radiotherapy	123	12 months ±9 (3-48)	>0.05
Total	132	12 months ±9 (3-48)	

SD: Standard deviation, min: Minimum, max: Maximum

Table 4. Ca 19-9 and CEA values

	Diagnosis time	In case of progression	Last visit moment	p
Tumour marker				
Ca19-9 [(ng/ml±SD) (min-max)]	5753±15250 (2-118000)	6542±14020 (3-100000)	7554±18596 (4-150000)	<0.001
CEA [(ng/ml±SD) (min-max)]	29±73 (1-500)	51±161 (0-1500)	48±150 (0-1500)	<0.001

CEA: Carcinoembryonic antigen, SD: Standard deviation, **min: Minimum, max: Maximum**

DISCUSSION

Pancreatic cancer accounts for 3% of all cancers. It is the fourth most common type of cancer for women and men.[13] It is a cancer type with the worst prognosis among all known cancers in the world, with 124000 newly diagnosed patients per year, with almost the same number of deaths, and with a five-year survival rate below 5%.[11] Pancreatic cancer is the ninth most common type of cancer in our country. Its annual incidence was found to be around 4.5/100,000.[2] The average survival after diagnosis is 3-6 months. Two-year survival is observed at only 10%. Mean survival with surgical resection has increased to 17-20 months. However, five-year survival does not exceed 10% despite resection.[14] Only 5-10% of pancreatic cancers are detected before the age of 60. 80% of the patients are over 60 years old.[10,15] Of 3138 Victorians diagnosed with pancreas ductal adenocarcinoma 2016-2019, 63% were metastatic at diagnosis. One-year survival increased between time periods, from 29.7% overall 2011-2015 (59.1% for non-metastatic, and 15.1% metastatic) to 32.5% overall 2016-2019 (p< 0.001), 61.2% non-metastatic (p=0.008), 15.7% metastatic (p=NS). A higher proportion of non-metastatic patients progressed to surgery (35% vs. 31%, p=0.020), and more received neoadjuvant therapy (16% vs. 4%, p<0.001).[13] In our study, most of our cases were found over 60 years of age (63.6%), which was consistent with the conduction data. Its incidence is higher in men than in women (mean 3/2).[16] The male/female ratio was found to be 79/53 in our study, which is consistent with the aforementioned data.

In our study, in accordance with the literature, when pancreatic adenocarcinomas were evaluated according to their localization, it was seen that 70.5% were located in the head, 19 in the trunk, and 10.5% in the tail. When the progression-free survival and overall survival times were evaluated according to tumour localization in our study; In accordance with the literature, the survival times of those with head localized tumours were found in the trunk and

tail was found to be longer than those located in the tail with statistical significance (p<0.001). Pancreatic cancer most commonly involves the pancreatic head. 60% of patients with pancreatic cancer are found in the head of the pancreas, 15% in the body, and 5% in the tail.[17,18]

In our study, it was found that 59 cases (44.7%) had no history of smoking, and 73 cases (55.3%) had no history of smoking. The median value of the number of packs smoked in the cases was 32 pack-years. Epidemiological studies show that smoking is associated with many types of cancer (e.g., stomach, oral cavity, oesophagus, larynx, bladder, kidney, pancreas, and cervix). 30% of pancreatic cancers occur due to smoking.[17]It is a known fact that smoking is a risk factor for pancreatic cancer. Pancreatic cancer incidence is 75% higher in smokers than non-smokers. The risk of developing pancreatic cancer continues for 10 years after quitting smoking. It is stated that smoking a pack of cigarettes a day for a year increases the risk of developing pancreatic cancer with 2%. The risk of pancreatic cancer development increases linearly with increasing dose.[18] Studies have emphasized that smoking increases pancreatic cancer and this is dose-dependent.[19,21] In one study, if all of Europe had stopped smoking at the beginning of the century; it has been stated that there will be a decrease in deaths due to pancreatic cancer per 150,000 people, and this decrease will be reflected as 30% in women and 45% in men. It has been reported that there will be 39000 fewer deaths due to pancreatic cancer.[20]

In our study, when the cases were analysed according to their alcohol use characteristics, it was observed that 10 (7.6%) of 132 subjects used alcohol, and 122 (92.4%) did not use alcohol. Since the history of alcohol was not adequately questioned in the history of the patients included in our study, sufficient information on alcohol use could not be obtained. Alcohol use is considered a risk factor for pancreatic cancer, but the risk associated with how much alcohol intake is unknown. In the study of Gupta et al.,[13] a relationship was found between the consumption of at least five glasses of alcohol per day and the risk of developing pancreatic cancer. In this study, it was stated that the risk of pancreatic cancer was found to be significantly higher, but it was not statistically significant. In some large epidemiological studies, alcohol has been found to be highly associated with pancreatic cancer. The American Department of Health for Men has stated that up to 28 grams of alcohol per day, and only half of it, can be used without the risk of developing cancer in women. Alcohol use is among the top 10 factor groups all over the world in terms of pancreatic cancer. It can be suggested that it may act as an auxiliary carcinogen as well as direct carcinogens such as alcohol, smoking and dietary factors.

In our study, it was determined that our pancreatic cancer cases had the most common type A blood (51.5%). Secondly, they had O blood group (29.5%). It was observed that our other pancreatic cancer cases had blood group B (14.5%) and blood group AB (4.5%). When the progression-free survival times of our cases were evaluated according to blood groups; The median is 3 months for those with blood group A (between 1 and 22 months), median 4 months (between 1-40 months) for those with blood group O, and 4.5 months (between 1-40 months) for those with blood group B and AB seen. In addition, overall survival is median 5 months (range 1-26 months) for blood group A, median 5 months (range 1-48 months) for blood group O, and median 6.5 months for blood group B and AB (1-48 months). When the survival times of our cases were evaluated according to blood groups, no statistically significant difference was found in terms of survival time (p>0.005).

It has been determined that ABO, one of the blood groups, is associated with pancreatic cancer. In the study conducted by Kim J et al.,[23] it was determined that people with A and AB blood groups have a higher risk of developing pancreatic cancer than those with O blood group. It has not been determined that those with blood group B have a higher risk of developing pancreatic cancer than those with blood group O. In the evaluation of patients with pancreatic cancer included in the study in terms of survival; one-year survival was 43%, three-year survival was 6%, and five-year survival was 2%. According to A, B, AB and O blood groups, the survival was determined as 9 months for those with A blood group, 9.0 months for those with B blood group, 9.1 months for those with AB blood group and 11.1 months for those with O blood group; no difference was found statistically significant among them. In the study of Greer et al.,[24] in the USA, compared to blood group 0; A, B, AB blood groups were found to have a high risk of developing pancreatic cancer.

They found that 131 patients with pancreatic cancer, especially those with A blood group, were statistically significantly higher at a rate of 47.63% when compared to the non-patient population and 277133 individuals with A blood group. 88 patients with blood type O, 32%. They found that it was statistically significantly lower when compared with the non-ill population with a ratio of 2 and 311795 individuals with O blood group 51%.[5] In our studyIt was determined that the highest rate of pancreatic cancer patients was in the A blood group with a ratio of 5 %, and the O blood group was the second with 29.5%. In the study, which was taken from 12 prospective studies by Wolpin et al.,[21] a control group of 1583 people was recruited against 1534 pancreatic cancer patients. When the blood groups of the patients were examined, 41.5% of the patients were in O blood group, 40.6% in A blood group, 12.3% in B blood group, 5.6% in AB blood group. In patients with pancreatic cancer, A, B, AB blood type is excluded. They found that those in the O blood group were higher than those in the O blood group, but this difference was not statistically significant. It has been stated that the risk of pancreatic cancer increases as the number of non-O alleles increases, and the risk increases the most especially in the BB genotype. Jihye Kim et al.[23] found that the increased risk associated with non-O blood groups was somewhat stronger among secretors than nonsecretors [ORs, 1.28 (95% CI, 1.15-1.42) and 1.17 (95% CI, 1.03-1.32) respectively; p interaction =0.002]. We did not find any interactions between ABO and Lewis antigens.

The most prominent symptoms of pancreatic cancer patients at admission are abdominal pain, weight loss and jaundice.[17,27] Among the complaints of our cases, the three most common main complaints, respectively, were jaundice (40.2%), vomiting (23.5%). and weight loss (22%). It is seen that our results are compatible with general literature knowledge. In the treatment of pancreatic cancer, one or more of the three treatment modalities, surgery, radiotherapy and chemotherapy, can be used in combination. Surgery is the only potential curative treatment method in pancreatic cancer.[24] The TNM Staging system is used to diagnose pancreatic cancer, determine prognosis, and shape treatment. Pancreatic cancer is usually detected at an advanced stage. In our study, 12 (9.1%) of the cases were found to be stage 2, 45 (34.1%) stage 3 and 75 (56.8%) stage 4 at the time of diagnosis.

In our study, when the progression-free survival of the patients in stage 2 is considered, the median is 12 months (between 4 and 40 months), the median survival of the patients in stage 3 is 5 months (between 1-12 months), and the median survival of the patients in stage 4 is 2 months (range 1 to 9 months). In terms of overall survival, patients in stage 2 have a median overall survival of 20 months (between 7 and 48 months), patients in stage 3 have a median survival of 8 months (between 1-18 months), and patients in stage 4 have a median survival of 3 months (between 1 and 20 months).

Progression-free survival and overall survival times by stage when evaluated; statistically significant difference was found. Accordingly, when the progression-free and overall survival times of the patients with stage 2 cancer were compared with the patients in stage 3 and 4 separately, they were found to be statistically significantly longer.

Whipple operation was performed in 45 (34%) of our cases, 41 (31%) were found to be inoperable, and 10 (7.5%) were unresectable. Less than 20% of pancreatic cancers are found to be curatively resectable at the time of diagnosis.[28]

In our study, in 20 of the patients (26 patients) who underwent EUS, the diagnosis and staging of EUS was found to be compatible with pathologies of computed tomography (CT) and pancreas and/or surrounding organs. In a study, out of 34 patients who had negative or suspicious results in terms of pancreatic cancer despite clinical suspicion on CT, a definitive diagnosis of pancreatic cancer was made in 88% of them by fine needle aspiration biopsy accompanied by EUS.[8]

In our study, it was seen that 61 of 132 patients were in Stage 2 and 3, 45 received adjuvant chemotherapy, 71 patients were Stage 4 and were evaluated as inop, and 26 received chemotherapy. Gemcitabine and cisplatin chemotherapy regimen were given to all those who accepted the treatment. When the progression-free survival times were evaluated according to the presence of chemotherapy, the progression-free survival and overall survival times were found to be statistically significantly longer in patients who received adjuvant chemotherapy at all stages, and in patients who were inoperable but did not receive chemotherapy. When the survival times were evaluated according to the presence of radiotherapy in the postoperative period; there was no statistically significant difference in terms of survival time.

Despite chemotherapy, the average survival time of pancreatic cancer patients with advanced disease is six months. Gemcitabine has been the standard systemic treatment agent in the palliative treatment of pancreatic cancer in the last 10 years, and its one-year survival rate was 18%. Although gemcitabine has been found to have clinical benefit in patients with pancreatic cancer, the five-year survival of patients is only 5%.[13] Calcer and Ellenberg did not give treatment to some of the 43 patients after curative surgery without metastasis, while they gave CRT to some of them. The application of CRT after surgery was found to be statistically significantly effective in this study. It was found that there was a significant difference between those who received adjuvant CRT at 20 months and those who only underwent surgery at 11 months.[18] In a retrospective study conducted by Corsini et al.,[13] it was found that post-surgical chemoradiotherapy increased survival at a statistically significant rate with 19.2 months versus 25.2 months compared to surgery alone

According to the European cancer research and treatment organization, adjuvant chemoradiotherapy has no effect on progression-free survival or overall survival. A progression-free survival of 17.4 months was found in the group receiving adjuvant chemoradiotherapy, whereas a progression-free survival of 16 months was found in the group receiving post-surgical chemoradiotherapy.[14] Pancreatic cancer treatment also varies according to the geography. While chemoradiotherapy is applied after chemotherapy in North America, chemotherapy alone is also preferred in Europe. At the time of diagnosis of pancreatic cancer, only 10-20% is detected while it is resectable. Chances of performing curative resection; It is 14%. The prognosis after resection is poor in pancreatic cancer without metastatic LN involvement. Three-year life expectancy is 27% and life expectancy duration is 15-19 months.[23]

Treatment for patients with localized pancreatic cancer Surgical resection combined with systemic chemotherapy is the cornerstone. In cases with extensive vascular involvement, Upfront surgery is considered suboptimal which can be classified as either borderline resectable pancreatic cancer or locally advanced pancreatic cancer. In these patients, FOLFIRINOX or gemcitabine plus nab-paclitaxel chemotherapy is currently used as preoperative chemotherapy and is eventually combined with radiotherapy.[8,24]

In patients with pancreatic cancer, EORTC applied 40 Gy radiotherapy with 5-FU in some patients after resection, and in some patients just followed up after resection. When these two groups are compared; found their survival as 17.1 versus 12.6 months, respectively.[24] ESPAC-1 administration of chemotherapy alone after resection, and after resection only after observation, the survival was found to be statistically significantly different at the level of 20.1 months versus 15.5 months, respectivel.[25] On the other hand, the mean survival of the arm receiving chemotherapy was found to be lower than in the observation; 15.9 months vs. 17.9 months, respectively.[27] According to RTOG 9704 made in the USA, it was compared to receiving radiotherapy with gemcitabine together with 5-FU versus receiving radiotherapy with only 5-FU and adding gemcitabine increased survival; 18.8 months vs. 16.7 month.[22] Oettle et al.[25] took 368 patients randomly resected for pancreatic cancer, gave some chemotherapy to gemcitabine, and only observed some of them. These two groups were followed for 6 months and a statistically significant difference in disease-free survival was found in the gemcitabine group versus the observed one, with 13.4 versus 6.9 months. When overall survival was considered, a difference was found at 22.1 versus 20.2 months. Among gemcitabine and 5-FU+ leukoverin, it was suggested to choose gemcitabine as an adjuvant therapy in CONKO-001,[25] ESPAC-3 [17] and RTOG 9704.[22] but studies on radiotherapy were inconclusive. It was emphasized that there was no statistically significant increase in survival in the ESPAC-3 study. In this study, it was emphasized that gemcitabine was more beneficial in terms of safety and dose intensity.[12]

In our study, in accordance with the literature, when the patients were evaluated according to their Ca 19-9 and CEA values; when the diagnosis/progression/last visit times were compared, it was observed that there was an increase in statistical significance from the diagnosis to the last visits. Some determinants have been studied to determine the response to treatment in pancreatic cancer. Ca 19-9 is the most prominently related. Ca 19-9 values were found to be significant in predicting response to treatment and is also effective in evaluating the response to treatment. It was determined that the average survival time of 424 patients with a diagnosis of pancreatic cancer who underwent surgical resection was 2.3 years for those with a Ca 19-9 value below 1000 before the operation, while the average survival time was 1.0 years for those with more than 100.[17] It has been found that there is a correlation between serum Ca 19-9 level and survival in patients receiving chemotherapy for pancreatic cancer. The serum tumour marker Ca 19-9 may be a useful prognostic factor for patients with advanced pancreatic cancer. Ca 19-9 can be used to predict tumour progression and survival. In a retrospective study by Boeck et al.,[27] it was found that Ca 19-9 had an effect on baseline values and values after CT or CRT, as well as progression-free survival and overall survival. They emphasized that Ca 19-9 is useful in determining progression-free survival and survival. Patients who have Ca 19-9 values at the time of diagnosis have a better prognosis than patients with high Ca 19-9 values at the beginning time.[27] One of the determinants studied to determine the response to treatment in pancreatic cancer is CEA. Other tumour markers such as CEA, Ca 125, pancreatic oncofetal antigen, ribonuclease, and elastase have not been shown to be useful in early diagnosis and follow-up.[17] However, in the study, it was determined that as the tumour mass increased, the CEA value also increased and was associated with a poor prognosis. CEA value was 5 mg/dl. It was determined that those who were above the age of six had a 1.4 times higher risk of death than those who were below the age of six.[29]

CONCLUSION

When the progression-free survival and overall survival times were evaluated according to tumour localization in our study; Survival times of those with head localized tumours are longer than those with trunk and tail localized tumours. When the progression-free survival and overall survival times are evaluated according to the stages; In terms of survival time, progression-free and overall survival times of patients with stage 2 cancers were found to be significantly longer when compared to patients with other stages. In our study, when the progression-free survival and overall survival times were evaluated according to the presence of chemotherapy, it was found that the progression-free survival and overall survival times in patients who received chemotherapy were statistically significantly longer in patients who received adjuvant chemotherapy at all stages, and in patients who were inoperable but did not receive chemotherapy. A statistically significant increase in Ca 19-9 and CEA values from diagnosis to the last visit was observed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Zonguldak Karaelmas (Bülent Ecevit) University Clinical Researches Ethics Committee (Date: 08.03.2011, Decision No: 2011/02).

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

Investigation of temporomandibular joint diseases and related factors in hemodialysis patients: a cross-sectional study

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ABSTRACT

Aims: This study aimed to investigate the prevalence of temporomandibular joint diseases (TMD) among hemodialysis (hd) patients and to explore the association between sociodemographic and laboratory parameters and the occurrence of TMD.

Methods: A cross-sectional study was conducted involving 81 hd patients. Sociodemographic characteristics and laboratory parameters of the participants were collected. TMD was assessed using the fonseca anamnestic test. Statistical analysis was performed using spss-22.

Results: Among the 81 participants, 39 (48.1%) were female and 42 (51.9%) were male, with a mean age of 58.2±15.27 years. TMD was detected in 50 patients (61.7%). Significant associations were found between TMD and the presence of comorbid diseases (p=0.002), low hemoglobin levels (p=0.001), and low albumin levels (p=0.002).

Conclusion: the study identified comorbid diseases, low hemoglobin, and low albumin as significant factors associated with TMD in hd patients. These findings suggest that heightened awareness and targeted management of these risk factors may improve clinical outcomes for hd patients with TMD. Enhanced understanding among clinicians regarding the high incidence and related factors of TMD in this patient population could lead to more effective treatment strategies.

Keywords: Fonseca anamnestic test, hemodialysis, temporomandibular joint diseases

INTRODUCTION

The temporomandibular joint (TMJ) is critical for daily activities such as speaking, swallowing, and chewing. Temporomandibular joint disease (TMD) refers to a range of clinical issues, including tmj pain, masticatory muscle disorders, intra-articular problems, and restricted mandibular movement.[1] TMD can encompass conditions such as osteoarthritis, rheumatoid arthritis, and other temporomandibular joint disorders.[2] Diagnosing TMD can be challenging due to overlapping symptoms with other conditions, such as jaw, face, and neck pain, difficulty chewing or speaking, and clicking or popping sounds in the joint. Therefore, a comprehensive evaluation is necessary to accurately diagnose TMD in hemodialysis (hd) patients.

TMD is relatively common in the general adult population, affecting approximately 3-15% of adults, with about 15% of these cases requiring treatment.[3] However, the incidence is notably higher in certain populations, such as hd patients, with up to 40% suffering from TMD.[4] Previous studies have explored the increased frequency of tmj disorders in conditions like polycystic ovarian syndrome, obesity, rheumatological diseases, and hashimoto's thyroiditis.[5-7] However, limited research has been conducted specifically on chronic kidney diseases (ckd) and hd patients. [7]

Hd is a common treatment for end-stage kidney failure (eskf), but it is associated with complications, including TMD.[8] Several factors may contribute to the development of TMD in hd patients, such as changes in bone metabolism, imbalances in calcium and phosphorus, and chronic inflammation. Additionally, the stress and strain from repeated venipunctures during hd may also play a role in the development of TMD.[4]

The Fonseca[8] anamnestic test is a tool used to assess the presence and severity of symptoms related to TMD in patients. Developed by Fonseca et al. in 2010, it has since been

widely used in clinical and research settings. Studies have demonstrated that the fonseca anamnestic test is a reliable and valid tool for assessing TMD symptoms.[9,10] It has also been used to evaluate the effectiveness of various treatments for TMD, such as physical therapy and splint therapy.[4-11]

According to the fonseca anamnestic test, common TMDs include myofascial pain, disc displacement with reduction, disc displacement without reduction, and arthritis. These conditions are classified based on the severity and type of symptoms reported by the patient.[8] It is important to note that the fonseca anamnestic test is just one diagnostic tool for TMD, and a proper diagnosis and treatment plan should be made by a healthcare professional experienced in managing TMD.[11] Overall, the fonseca anamnestic test is a valuable tool for assessing TMD symptoms, helping clinicians and researchers better understand and treat this common condition.

Treatment for TMD in hd patients depends on the type and severity of the disorder. Conservative measures such as physical therapy, pain management, and lifestyle modifications may be effective for mild cases, while severe cases may require surgery or other interventions.[4]

In this cross-sectional study, we aimed to determine the prevalence of TMD and its associated clinical and biochemical factors using the fonseca anamnestic test in hd patients. Additionally, we will discuss the diagnosis and treatment of TMD in this patient population. A better understanding of TMD in hd patients is essential for developing effective management strategies and improving patient outcomes.

METHODS

Ethical considerations

Prior to participation, all patients were informed about the study objectives, procedures, and potential risks and benefits. Written informed consent was obtained from each participant. The study protocol was reviewed and approved by the scientific Mardin Artuklu University Clinical Researches Ethics Committee (Date: 10.07.2023, Decision No: 2023/7-19) and adhered to the ethical standards set forth in the 1964 Declaration of Helsinki.

Study design and participants

This cross-sectional study was conducted with 81 hd patients from three hd centers located in mardin, Turkiye. The study population included patients aged 18 years and older who were receiving regular hd treatment. Patients with elevated C-reactive protein (CRP) levels, indicating inflammation, or those with active malignancies were excluded to avoid confounding factors that could influence the presence of TMD.

Data collection

Data were collected through direct interviews and review of medical records. Sociodemographic information, including age, gender, duration of hd treatment, and relevant medical history, were recorded. Biochemical parameters from the past month, such as CRP, albumin, ferritin, and hemoglobin levels, were also obtained from the patients' medical records. The threshold value for bmi was set at 30 kg/m². This value was chosen to align with internationally recognized definitions of obesity by health organizations and standardized health guidelines in previous literature.

Assessment of TMD

The fonseca anamnestic test, a validated self-reported questionnaire, was utilized to assess the presence and severity of TMD. This test consists of ten questions addressing symptoms related to TMD, including pain in the temporomandibular joint, limitations in jaw movement, and other associated symptoms. Each question is scored on a scale from 0 to 4, with higher scores indicating greater severity of symptoms. The total score ranges from 0 to 40, with higher scores indicating more severe TMD symptoms. Based on the responses and following the dentist's tmj examination, patients were categorized as having TMD, or no TMD.

Grouping of Participants

Participants were divided into two groups based on the presence of TMD as determined by the fonseca anamnestic test:

TMD group: Patients who reported symptoms indicative of TMD.

Non-TMD group: Patients who did not report symptoms indicative of TMD.

The collected data were analyzed to determine the prevalence of TMD among the hd patients and to explore potential associations between TMD and various sociodemographic and biochemical factors. Comparative analyses were conducted between the TMD and non-TMD groups to identify any significant differences.

Limitations

This study has several limitations. Firstly, the sample size is limited, and a larger sample could enhance the generalizability of the results. The study sample was selected solely from hd centers in mardin, and therefore, the findings may not be generalizable to hd patients in other geographical regions. Additionally, as this study has a cross-sectional design, it is not possible to determine a causal relationship between TMD and hd. The evaluation of TMD was conducted using only the fonseca anamnestic test, and the subjective nature of this test may introduce some biases. The observation period of the study is limited, which may hinder the assessment of long-term outcomes of TMD. Lastly, some clinical and biochemical data may be missing or insufficient, which could affect the accuracy of the results.

Statistical Analysis

Independent t-tests were employed to compare normally distributed variables in the statistical analysis of the data, specifically for comparing means between two groups. For variables that did not follow a normal distribution, the Mann-Whitney U test was used to compare two independent groups. To analyze categorical data, the fisher's exact test was employed to assess the association between categorical variables. A significance level of $p<0.05$ was adopted to determine statistical significance throughout the analyses.

Furthermore, a power analysis was conducted to determine the necessary sample size for the study, ensuring adequate statistical power to detect meaningful differences between groups. This step is crucial for ensuring the reliability and validity of the study's findings. Statistical analyses were performed using spss 22.0 (statistical package for the social sciences), an ibm software program widely used for statistical analysis in research settings.

RESULTS

Thirty-nine (48.1%) of the participants were female and 42 (51.9%) were male. The mean age was 58.2±15.27 years. After the fonseca anamnestic test evaluation was performed to determine the severity of TMD in patients, 31 (38.3%) patients did not have TMD, whereas TMD was found in 50 (61.7%) patients (Table 1).

In our study, when comparing the sociodemographic and biochemical parameters of hd patients with and without TMD, TMD was found in 42 (72.4%) of those with comorbid disease (p=0.002). The hemoglobin level was 10.67±1 g/dL in patients without TMD, whereas it was significantly lower at 9.9±0.84 g/dL in patients with TMD (p=0.001). Similarly, the albumin level was 3.78±0.4 g/L in patients without TMD, but it was lower at 3.5±0.37 g/L in patients with TMD (p=0.002) (Table 2). Anova and kruskal-wallis tests were not employed in this study.

Table 1. Sociodemographic characteristics of hemodialysis patients

	n: 81
Age (mean±SD)	58.20±15.27
Sex, n (%)	
Female	39 (48.10)
Male	42 (51.90)
Height (cm), mean±SD	163.20±15.80
Weight (kg), mean±SD	70.20±17.40
BMI, (kg/m²)	
<30	58 (71.60)
>30	23 (28.40)
Hemodialysis time (month), n (%)	
0-12 months	29 (35.80)
13-60 months	30 (37)
>60 months	22 (27.20)
Alcohol/smoking, n (%)	
No	57 (70.40)
Yes	24 (29.60)
Comorbidities, n (%)	
No	20 (24.70)
Yes	61 (75.30)
Educationalstatus, n (%)	
Illiterate	22 (27.20)
Primary education	36 (44.40)
Secondary education	21 (25.90)
high education	2 (2.50)
Marital status, n (%)	
Single	16 (19.80)
Married	65 (80.20)
Lifestyle, n (%)	
Alone	8 (9.90)
With his wife/her husband	19 (23.50)
With his wife/her husband and children	36 (44.40)
With their children	10 (12.30)
With mom and dad	8 (9.90)
Place of residence, n (%)	
Rural	14 (17.30)
Urban	67 (82.70)
Working condition, n (%)	
Working	6 (7.4)
Not working	75 (92.60)
TMD, n (%)	
No	31 (38.30)
Yes	50 (61.70)
Hemoglobin	10.19±0.97
Ferritin	574.36±399.57
Albumin	3.58±0.41
CRP	18.58±17.61
Pth	504.47±479.99
Kt/v	1.39±0.19
URR	71.03±7.73

SD: Standard deviation, BMI: Body-mass index, TMD: Temporomandibular joint disease, CRP: C-reactive protein, PTH: Parathormone, URR: Urea reduction ratio (urea reduction rate), kt/v: urea clearance x treatment time/total body water volume, statistical tests used: independent t-test, Mann-Whitney U and Fisher's exact test

DISCUSSION

Research on TMD in predialysis ckd and hd patients remains limited, often involving detailed and costly examinations.[12] In order to overcome these difficulties and evaluate the relevant clinical and biochemical factors, our study attempted to determine the prevalence of TMD using the fonseca anamnestic test. In our study, we found a significant difference in the prevalence of TMD between hd patients and the general population, and we identified significant relationships between TMD and factors associated with hd treatment. Yilmaz et al.[4] reported a high TMD prevalence of 41.5% among hd patients, significantly higher than in the control group. They observed statistically significant increases in CRP, pth, bmi, and decreases in albumin and hemoglobin levels among those with TMD. Additionally, they noted a higher prevalence of TMD among women compared to men. In our study, we found the presence of TMD in hd patients to be as high as 61.7%. However, we did not find any statistical difference between men and women. Another study focusing on predialysis ckd patients found that 40.6% had myogenic TMD, associated with elevated CRP, ferritin, pth, and decreased albumin and hemoglobin levels.[5] These findings underscore the multifaceted nature of TMD in kidney disease populations, suggesting potential links between TMD and systemic inflammation, metabolic disturbances, and gender-specific differences.[13] Despite the high prevalence observed in our study and others, the specific mechanisms underlying TMD development in hd and ckd patients warrant further investigation. Our investigation highlighted a notable association between TMD and comorbidities, with patients exhibiting significantly lower hemoglobin and albumin levels when TMD was present. This correlation underscores the likelihood that TMD contributes to decreased hemoglobin and albumin levels through interconnected mechanisms.

Chronic pain associated with TMD often leads to reduced food intake and nutritional deficiencies, which are crucial for albumin synthesis and hemoglobin production. Studies have demonstrated that chronic pain conditions like TMD are linked to systemic inflammation, which can influence iron metabolism and hemoglobin levels over time.[14] Moreover, inflammation within the tmj and surrounding tissues triggers systemic responses that disrupt metabolic processes and

Table 2. Comparison of sociodemographic and biochemical parameters of hemodialysis patients with and without temporomandibular joint disease

	TMD (-)	TMD (+)	p value
Age (mean±SD)	57.94±12.28	58.36±16.98	0.904
Sex, n (%)			
Female	13 (%33.30)	26 (%66.70)	0.378
Male	18 (%42.90)	24 (%57.10)	
BMI, kg/m²	27.70±5.80	26.20±5.10	0.239
Hemodialysis time (month), n (%)			
0-12 months	13 (%44.80)	16 (%55.20)	0.482
13-60 months	9 (%30)	21 (%70)	
>60 months	9 (%40.90)	13 (%59.10)	
Alcohol/smoking			
No	23 (%40.40)	34 (%59.60)	0.53
Yes	8 (%33.30)	16 (%66.70)	
Comorbidities			
No	15(%65.20)	8 (%34.80)	0.002
Yes	16 (%27.60)	42 (%72.40)	
Educationalstatus			
Illiterate	11 (%50)	11 (%50)	0.339
Primary education	14 (%3.90)	22 (%61.10)	
Secondary education	6 (%28.60)	15 (%71.40)	
High education	0 (%0)	2 (%100)	
Marital status, n (%)			
Single	6 (%37.50)	10 (%6.50)	0.943
Married	25 (%38.50)	40 (%61.50)	
Lifestyle, n (%)			
Alone	2 (%25)	6 (%75)	0.827
With his wife/her husband	8 (%42.10)	11 (%57.90)	
With wife/husband and children	15 (%41.70)	21 (%58.30)	
With their children	4 (%40)	6 (%60)	
With mom and dad	2 (%25)	6 (%75)	
Place of residence, n (%)			
Rural	4 (%28.60)	10 (%71.40)	0.412
Urban	27 (%40.30)	40 (%59.70)	
Working condition			
Working	1 (%16.70)	5 (%83.30)	0.258
Not working	30 (%40)	45(%60)	
Hemoglobin	10.67±1	9.9±0.84	0.001
Ferritin	471.40±363.30	638.10±411	0.068
Albumin	3.78 ±0.40	3.50±0.37	0.002
CRP	19.54±19.98	17.98±16.14	0.701
PTH	503.06±507.76	505.34±467.22	0.984
Kt/v	1.40±0.17	1.39±0.20	0.788
URR	70.91±7.38	71.11±8.02	0.908

SD: Standart deviation, BMI: Body-mass index, TMD: temporomandibular joint disease, CRP: C- reactive protein, PTH: parathormone, URR: Urea reduction ratio (urea reduction rate), kt/v: urea clearance x treatment time / total body water volume, **statistical tests used:** independent t-test, Mann-Whitney U and Fisher's exact test

alter protein metabolism, further contributing to decreased albumin levels.[15] These insights emphasize the necessity for comprehensive management strategies addressing both pain relief and nutritional support in patients with TMD, with surgical intervention considered for severe cases.[16]

Various factors, including age, gender, duration of hd, metabolic disturbances, and medication use, contribute to the development of TMD in these patients. Our study identified comorbidities, low hemoglobin, and low albumin levels as risk factors associated with increased prevalence of TMD.

Several studies have proposed conservative treatments, such as physical therapy, pharmacotherapy, and occlusal splint therapy, as effective approaches for managing TMD in hd patients.[17-19] However, the precise causal relationship and specific risk factors linking TMD and hd remain unclear, necessitating further research. It is important to acknowledge several limitations of our study. The relatively small sample size limits the generalizability of our findings, and the cross-sectional design precludes establishing causality. Future longitudinal studies are warranted to investigate the causal relationships between identified risk factors and TMD in hd patients more effectively. Understanding TMD's impact on patients undergoing hd is crucial for developing tailored management strategies aimed at improving patient outcomes.

CONCLUSION

TMD are prevalent in hd, and the incidence of these disorders is higher in hd patients compared to the general population. Early detection and treatment of these disorders can improve the quality of life of hd patients. Further research is needed to explore the pathophysiology of TMD in hd patients and to develop new and effective treatment strategies. Therefore, it is recommended that hd patients undergo routine dental examinations to detect and treat TMD early on.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Mardin Artuklu University Clinical Researches Ethics Committee (Date: 10.07.2023, Decision No: 2023/7-19).

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. The study was presented as an oral presentation at the 5th Internal Medicine Congress of the University of Health Sciences held in Antalya on 04.06.2022.

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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

Evaluation of transmission routes in patients with acute hepatitis B

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ABSTRACT

Aims: In this study, we aimed to determine the possible transmission routes in patients diagnosed with acute hepatitis B virus (HBV) infection by anamnesis, physical examination and serologic tests.

Methods: For this purpose, 44 patients hospitalized with acute hepatitis B in the Infectious Diseases and Clinical Microbiology Clinic of Ankara Numune Training and Research Hospital were included in the study. Patients were questioned about possible transmission routes. The diagnosis of acute hepatitis B was based on anamnesis, physical examination findings, anti-HBcIgM positivity by ELISA, absence of HBsAg positivity for more than 6 months and an increase in liver enzymes AST and ALT values 8-10 times above normal levels. HBsAg, HBeAg, AntiHBe serologic tests and Anti-HDV antibody against hepatitis delta virus (HDV) were also investigated in the sera of patients with acute hepatitis B. Possible transmission forms were questioned and recorded in the patient follow-up forms. All serologic markers were analyzed by ELISA (Organon, Netherlands).

Results: Of the 44 patients included in the study, 29 (66%) were male and 19 (34%) were female. The mean ages of male and female patients were 36.6 (24-66 years) and 31.6 (23-60 years), respectively. When the patients with acute hepatitis B were evaluated in terms of possible transmission routes, 8 (18.2%) of the patients had HBsAg positive spouses, 3 patients had a history of surgical intervention in the last 6 months, 3 patients had a history of dental intervention, 2 patients had a history of blood transfusion in the last 6 months, and 2 patients had more than one possible transmission risk. Twenty-six (59.3%) patients had no possible route of transmission.

Conclusion: Our findings revealed that possible transmission routes could not be identified in more than half of acute hepatitis B patients. In addition, we determined that 18.2% HBsAg positivity in the spouses of acute hepatitis B patients may be a possible route of transmission. In conclusion, we believe that patients with acute HBV infection should be evaluated for possible transmission routes, family members of acute hepatitis B patients should be screened for HBV infection, those with negative anti-HBs antibodies should be vaccinated, and relatives of HBsAg positive patients should be checked periodically.

Keywords: Acute hepatitis B, transmission routes, Anti-HBc IgM, transaminase enzymes

INTRODUCTION

Hepatitis B virus (HBV) infection is an important public health problem worldwide.[1] Hepatitis B virus can cause both acute and chronic disease. The World Health Organization (WHO) estimates that 254 million people will be living with chronic hepatitis B infection in 2022, and 1.2 million new HBV infections will occur each year. According to WHO data, HBV infection caused an estimated 1.1 million deaths in 2022, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer).[2] Hepatitis B and hepatitis C viruses are the leading causes of liver cirrhosis and liver cancer and are important causes of mortality and morbidity.[3]

HBV is a DNA virus transmitted to humans parenterally (with blood and blood products), transplacentally, postnatally (from mother to child), percutaneously, sexually, horizontally (transmission between family members) or by close contact.[1,4] Primary HBV infection is an infection that can only be transmitted from infected individuals to other people, and it can be self-limiting, self-resolving or lifelong. HBV is an important cause of fulminant hepatitis, chronic liver disease, cirrhosis, and hepatocellular cancer.[5-7]

There are approximately four million patients with hepatitis B virus infection in Turkiye. The worldwide distribution of the infection is categorized into three groups: prevalence of chronic HBV infection, overall infection rate, age at acquisition of infection and the most common route of transmission. In highly endemic areas, more than 10% of the population is infected with HBV. In moderately endemic areas, the prevalence of chronic HBV infection is between

2-10%. In low endemic areas, carriage is less than 2%. According to WHO data, Turkiye is included in moderately endemic regions with 2-8% HbsAg positivity.[8]

In a study conducted by the Turkish Liver Research Association (TKAD) in 2009 in which 5,471 individuals were screened, HBsAg positivity was reported as 4.0%, anti-HBs positivity as 32.0% and anti-HBc total positivity as 30.6%. The anti-HBe positivity rate in HBsAg positive patients was reported as 92.1%.[9] The risk groups for percutaneously transmitted HBV include infants of carrier mothers, spouses and family members of carriers, polygamists such as homosexuals or prostitutes, intravenous drug addicts, hemodialysis patients, patients living in nursing homes, immunocompromised patients and healthcare personnel.

In this study, we aimed to determine the possible transmission routes in patients with acute viral hepatitis B (AVHB) diagnosed by anamnesis, physical examination and laboratory tests who were hospitalized in Ankara Numune Training and Research Hospital.

METHODS

This article is based on a specialty thesis completed in 2000. No ethics committee decision was taken at that time. In this thesis study was conducted with the approval of the institution. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted in 44 patients with acute viral hepatitis B (AVHB) who were hospitalized in the Infectious Diseases and Clinical Microbiology Clinic of Ankara Numune Training and Research Hospital. Only patients diagnosed with acute hepatitis B were included in the study, chronic hepatitis B patients and inactive HBsAg carriers were excluded from the study. For the diagnosis of acute hepatitis B, anamnesis, physical examination findings, serum transaminase values 8-10 times higher than normal and anti-HBc IgM positivity were required. Data on age, gender, occupation, hospitalization and discharge dates and HBsAg, Anti-HBc IgM, HBeAg, Anti-HBe, Delta Ag and Anti-Delta markers were recorded. Possible transmission forms were questioned and recorded in the patient follow-up forms. All serologic markers were studied by ELISA (Organon, Netherlands) method.[10]

RESULTS

Of the patients included in the study, 29 were male (66%) and 15 were female (34%) ($p<0.05$). The mean age was 34.9 years and the age range was 23-66 years. The mean age was 36.6 years in the male group and 31.6 years in the female group. The distribution and mean age of patients hospitalized with acute hepatitis B according to gender are shown in Table 1.

The evaluation of AVHD patients in terms of possible transmission routes is shown in Table 2.

Table 1. Gender distribution and mean age of patients hospitalized with acute hepatitis B

Gender	Number (%)	Average age	Minimum-maximum
Male	29 (66)	36.6	24-66
Famele	15 (34)	31.6	23-60
Total	44 (100)	34.9	23-66

Table 2. Evaluation of AVHD patients in terms of possible transmission routes

Possible transmission routes	Number (%)
HBsAg positivity in spouse	8 (18.2)
History of dental intervention	3 (6.8)
History of surgical intervention in the last 6 months	3 (6.8)
Blood transfusion in the last 6 months	2 (4.5)
Multiple possible transmission risks	2 (4.5)
Possible transmission route undetermined	26 (59.3)
Total	44 (100)

Anti-HBc IgM was positive in all 44 patients with acute hepatitis B included in the study. HBsAg was positive in all but one patient. The HBsAg negative patient was considered as acute hepatitis B infection during the window period. Anti-HBe antibody was positive in 19 (43%) patients. The age, gender and serologic test results of the patients with AHD are shown in Table 3.

None of our AVHD patients had fulminant hepatitis or cholestatic course during clinical follow-up. Since long-term follow-up of the patients could not be performed, chronicization or inactive carrier rates could not be determined.

DISCUSSION

Following an incubation period of 60-180 days, acute hepatitis B virus infection can be seen in four different forms: icteric, anicteric, cholestatic and fulminant forms. In 5-20% of adults infected with hepatitis B virus, acute

While hepatitis symptoms occur, 65-80% may present as a subclinical infection or anicteric hepatitis picture.[11]

The rate of chronicization in acute hepatitis B infection varies depending on factors such as age, gender, anicteric form and presence of immunosuppressive status and this rate has been reported to be between 5-10% in adults.[7,12]

Çavuşlu et al.[13] evaluated 101 patients with acute hepatitis B. Fulminant hepatitis was observed in 3 cases and cholestatic course was observed in 3 cases. In the present study, we found HBsAg positivity in 9 (20.4%) of the spouses of patients with AVHD. None of our AVHD patients had fulminant hepatitis or cholestatic course during the follow-up period. Since long-term follow-up could not be performed, we could not determine how many of the patients became chronic.

The main transmission routes of HBV are parenteral transmission, sexual transmission, vertical transmission from mother to infant and horizontal transmission between family members.[14] In developing countries, vertical transmission (transmission from infected mother to newborn) and horizontal transmission (especially domestic contact with infected individuals) play an important role.[15]

The most important source of parenteral transmission is contact with blood and body fluids of HBV-infected patients. Parenteral transmission can be seen especially in those who use intravenous drugs with a common syringe, contaminated sharps injuries, tattooing, acupuncture, ear piercing, circumcision which may cause bleeding, use of common objects (toothbrush, razor blade, nail scissors), injector sticks.

Table 3. Age, gender and serologic test results of AVHD patients

Sequence No	Age	Gender	HBsAg	Anti HBclgM	HBeAg	Anti-Hbe	Anti Delta
1	28	E	+	+	+	-	-
2	60	K	+	+	-	-	-
3	24	E	+	+	-	-	-
4	34	E	+	+	-	-	
5	31	E	+	+	+	-	-
6	23	K	+	+	-	-	-
7	25	E	+	+	-	+	-
8	49	E	+	+	--	+	-
9	27	K	+	+	-	+	-
10	26	K	+	+	-	+	-
11	52	E	+	+	-	+	-
12	38	K	+	+	-	+	-
13	30	K	+	+	-	-	-
14	24	E	+	+	+	-	-
15	18	K	+	+	+	-	-
16	25	E	+	+	-	-	-
17	24	K	+	+	+	-	-
18	34	E	-	+	+	-	-
19	42	E	+	+	+	-	-
20	32	E	+	+	+	-	-
21	40	E	+	+	-	+	-
22	33	E	+	+	-	+	-
23	27	E	+	+	-	+	-
24	28	E	+	+	-	+	-
25	27	E	+	+	-	+	-
26	24	E	+	+	-	+	-
27	29	K	+	+	-	-	-
28	31	E	+	+	-	-	-
29	26	K	+	+	--	+	-
30	60	E	+	+	-	+	-
31	26	E	+	+	+	-	-
32	43	K	+	+	-	+	-
33	27	E	+	+	+	-	-
34	62	E	+	+	-	+	-
35	32	K	+	+	-	-	-
36	66	E	+	+	+	-	+
37	58	E	+	+	+	-	-
38	49	E	+	+	-	+	+
39	52	K	+	+	-	+	-
40	42	E	+	+	+	-	-
41	24	K	+	+	-	+	-
42	23	K	+	+	-	-	+
43	33	E	+	+	+	-	-
44	29	E	+	+	+	-	-

In addition, parenteral transmission is also possible through transfusion of infected blood and blood products.[14] The most common route of transmission of HBV in hemodialysis patients is parenteral transmission.[16]

Apart from parenteral transmission, hepatitis B infection can also be transmitted sexually, from mother to infant via vertical transmission, transplacental transmission or in the postnatal period.[4] In a study conducted in 10 centers in Turkiye, Mıstık et al.[17] reported HBsAg positivity as 9.2% in the spouses of patients with acute hepatitis B. In our study, HBsAg positivity was found in 9 (20.4%) and Anti-HBs positivity was found in 14 (31.8%) spouses of patients with AHBV.

In a study conducted by Kılıçturgay et al.,[18] the rate of HBsAg positivity in the spouses of patients with hepatitis B was reported as 13.5%. In another study conducted in Turkiye, the rate of HBsAg positivity in family members of HBsAg positive patients was reported as 12.3%.[19] In our study, the possible transmission risk of surgical and dental procedures alone was determined as 6.8% and 6.8%, respectively. In the study of Mıstık et al.,[17] the transmission risk rates of dental and surgical procedures were reported as 13.2% and 8.8%, respectively.

In a study conducted by Kılıçturgay et al.[18] in 192 cases of acute hepatitis B, the rate of dental intervention as a possible route of transmission was reported as 9.3%. In the present study, blood transfusion in the last 6 months as a possible route of transmission was found to be 4.5%. In the study of Mıstık et al.,[17] the rate of possible transmission by blood transfusion was reported as 4% and in the study of Kılıçturgay et al.,[18] the rate was reported as 4.6%. Horizontal transmission is the transmission of the virus between family members within the household without demonstrable parenteral, sexual or perinatal transmission. Horizontal transmission is thought to be the result of contact of body fluids such as infected blood, saliva, etc. with defective skin.[19] In the study by Mıstık et al.,[17] this rate was reported to be 44.4%, while this rate was reported to be 40% in the study by Kılıçturgay et al.[18]

Baş[20] reported HBsAg positivity in the spouses of 184 (22.4%) of the patients in a study conducted in 820 chronic hepatitis B and inactive hepatitis B carrier patients. It was reported that this low rate may be due to pre-marital screening and vaccination of the spouses of HBsAg positive cases. It was also reported that sexual transmission may be a possible cause of this transmission. In the same study, when the patients were evaluated in terms of the use of common items at home, it was reported that using the same towel ranked first with 83.2%, followed by using the same razor and nail clippers with 79.3% and using the same kitchen utensils with 69.8%. HBV contamination of shared items may be a possible factor in horizontal transmission within the household. In the present study, the rate of HBsAg positivity found in nine (20.4%) of the spouses of 44 patients with AVHD was similar to the rate of 22.4% reported by Baş.

Alkan et al.[21] evaluated the risk factors for possible transmission and chronicization rates in 48 patients with AVHD. In the study, family history of hepatitis B in 9 (18.8%) patients, suspicious sexual contact in 6 (12.5%), history of blood transfusion in 6 (12.5%), mucosal or cutaneous contact with infected blood and body fluids in 5 (10.4%), working in a risky job (health worker, nursing home staff) in 3 (6.3%), hemodialysis treatment in 2 (4.2%), tattooing in 2 (4.2%) were reported as possible risk factors. In the same study, possible risk factors could not be determined in 12 (25%) patients and it was reported that 4 (8.9%) of the patients developed chronic HBV infection. In our study, the rate of patients whose possible route of transmission could not be determined (59.3%) was higher than the rate reported by Alkan et al.[21]

Dığrak and Tezel[22] investigated the knowledge and attitudes of patients about HBV in a questionnaire study conducted in 244 HBsAg positive male patients. The source of information was reported as health personnel in 51.9% of the patients. While 88.4% of the respondents correctly answered that HBV can be transmitted through blood, the rate of those who correctly knew that vaccination protects against the disease was reported as 80.7%.

Limitations

Since long-term follow-up of AVHb patients could not be performed in our study, it could not be determined how many of the patients developed chronic hepatitis B and how many developed inactive carriages.

CONCLUSION

Patients with acute HBV infection should be evaluated for possible transmission routes, family members of patients with acute hepatitis B should be screened for HBV infection and informed about transmission routes, and those with negative anti-HBs antibody should be vaccinated. In addition, we believe that periodic control of the relatives of HBsAg positive patients may prevent long-term complications related to HBV.

ETHICAL DECLARATIONS

Ethics Committee Approval

This article is based on a specialty thesis completed in 2000. No ethics committee decision was taken at that time. In this thesis study was conducted with the approval of the institution.

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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Review

General approach to hemoptysis

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ABSTRACT

Hemoptysis is bleeding from the mouth originating from the lungs or bronchi. It is one of the most important symptoms in chest diseases that leads to urgent admission and requires urgent intervention. Massive hemoptysis is defined as any life-threatening bleeding. Although an expected blood volume of more than 600 ml in 24 hours is often defined as massive hemoptysis, there is no universally accepted specific volume amount.The source of bleeding and its associated causes are frequently not readily identifiable, and the approach to managing this critical condition demands a swift intervention. In contrast to hemorrhage in various settings, even a minimal quantity of blood can quickly obstruct the airways, hindering both oxygen delivery and ventilation, which may result in asphyxiation and subsequent cardiovascular failure. Prioritizing the prompt management of the patient's airway and the immediate cessation of bleeding is crucial in efforts to identify and mitigate the hemorrhage. A well-coordinated team effort is vital to maximize the likelihood of patient survival.

Keywords: Hemoptysis, etiology, diagnosis, treatment

INTRODUCTION

Hemoptysis is the bleeding from the mouth originating from the pulmonary or bronchial vascular system. In other words, it is defined as the expulsion of blood through the mouth from a source located below the glottis level.[1,2] It is a symptom that generally causes panic in patients, causes them to seek medical attention immediately, and requires close monitoring.[3] Hemoptysis is held responsible for 6-8% of patients applying to chest diseases outpatient clinics and 11% of admissions to chest diseases services.[2] 50% of hemoptysis cases are mild, self-limiting, and have a good prognosis with conservative treatment. However, the mortality rate of massive hemoptysis cases is 50% .[2]

Hemoptysis is defined in terms of quantity as mild, moderate, severe and massive. Mild hemoptysis is defined as <100 ml in 24 hours, moderate hemoptysis as 100-600 ml in 24 hours, and massive hemoptysis as >600 ml/24 hours. The patient may swallow or aspirate some of the blood. Although it is generally defined as massive hemoptysis when the amount of blood expected in 24 hours is more than 600 ml, there is no specific amount that is universally accepted.[4,5] As a result, any hemoptysis that causes respiratory failure should be considered life-threatening hemoptysis.

In most patients, hemoptysis is minimal and resolves spontaneously. Massive hemoptysis is generally defined as the expectoration of a large amount of blood and/or rapid bleeding and is seen in rates ranging from 5% to 14% of patients.[4,6] The cause of death in massive hemoptysis is asphyxia rather than blood loss. Additionally, blood loss sufficient to cause cardiovascular collapse often results in death. Therefore, the mortality rate (50%) is generally higher in patients with massive hemoptysis that cannot be treated immediately.[7]

PATHOPHYSIOLOGY

Pulmonary vascular nutrition is provided by bronchial and pulmonary arteries. 99% of the blood going to the lungs is provided by the pulmonary arteries. The bronchial arterial system provides nutrition to the extra- and intrapulmonary airways and pulmonary vascular structures without providing gas exchange. It also helps feed the mediastinal lymph nodes, nerves, visceral pleura, esophagus and aorta through their vasovasorum. Pulmonary and bronchial arteries interact through microscopic anastomoses.[6] When the pulmonary circulation is under pressure due to reasons such as thromboembolic diseases, vasculitic disorders or

hypoxic vasoconstriction, the blood flow provided by the surrounding anastomoses to the bronchial arteries increases. The wall of the bronchial arteries becomes hypertophic, increasing the possibility of bleeding into the bronchi and alveoli.[2,6]

While hemoptysis originating from the low-pressure pulmonary system causes low blood loss, bleeding from the high-pressure bronchial artery originating from the systemic artery is higher.[3]

While 90% of severe hemoptysis cases requiring treatment originate from the bronchial artery, 5% originate from the pulmonary artery. The remaining 5% consists of nonbronchial systemic arterial bleeding. Hemoptysis may also originate from nonbronchial systemic arteries due to revascularizations occurring in pleural adhesion areas and along the pulmonary ligaments caused by chronic inflammatory processes, and anastomoses with the pulmonary arterial circulation. It has also been shown that bleeding from the bronchial artery in a patient may be accompanied by bleeding from nonbronchial and pulmonary arteries. Hemoptysis, although rare, may originate from the pulmonary vein, bronchial vein and capillary (Figure 1).[2,3]

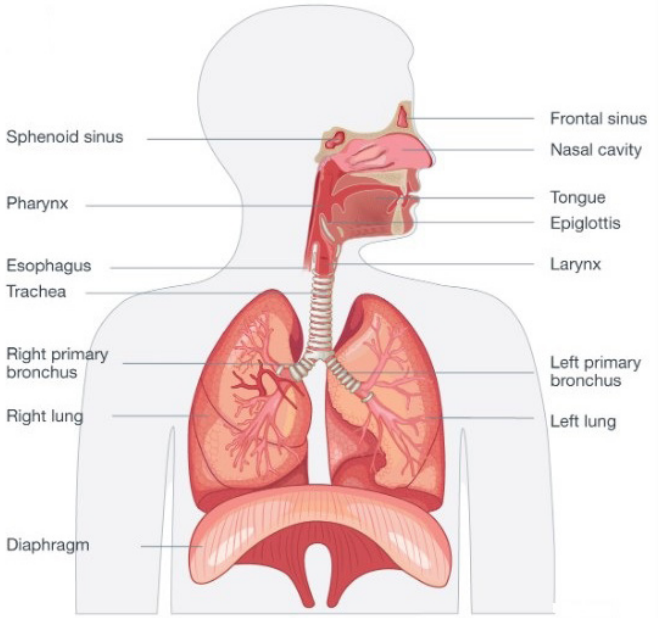

Figure 1. Human-respiratory-system

Information from https://openmd.com/guide/human-respiratory-system

ETIOLOGY

The causes of hemoptysis vary depending on patient characteristics, geographical region, time period, and diagnostic techniques.[2,6,7] Determination of etiology is important in hemoptysis. If hemoptysis is suspected, it should first be questioned whether the blood actually comes from the respiratory system. Anamnesis helps determine the anatomical location of bleeding and distinguish between hemoptysis and pseudohemoptysis. Nasopharyngeal or gastrointestinal causes must be excluded in patients presenting with hemoptysis. To ensure that bleeding is subglottic, the oral cavity and nasal cavity should be examined, taking into account that nasal or gingival bleeding overnight may result in hemoptysis the next morning (Table 1).[2,8]

The most common cause of hemoptysis worldwide is tuberculosis.[9-11] The most common cause of hemoptysis in patients between the ages of 40 and 60 is lung cancer, and it has been reported that the risk of malignancy is high in this age group, especially in smokers.[12,13] While in developed countries, acute bronchitis, bronchiectasis, fungal infections such as aspergiloma and cocaine-related pathologies are detected in patients with hemoptysis, pneumonia, bronchiectasis and tuberculosis are also observed in developing countries.[1,6,13] The causes of hemoptysis in our country are listed as bronchiectasis, bronchial carcinoma, tuberculosis and pneumonia.[14]

Other factors seen in hemoptysis are pulmonary embolism, aspergilloma staph aerus, pseudomonas aeriginosa, hydatid cyst, influenza, HIV, hypertension and CHF.[15]

Infections are the most common cause of hemoptysis, accounting for approximately 60-70%. Due to infection, inflammation and edema develop on the mucosal surface, causing superficial blood vessels to cracking.[2,3] Hemoptysis due to bronchiectasis usually requires hospitalization.[16]

Bronchogenic carcinomas constitute 5-44% of lung cancer responsible for hemoptysis. Hemoptysis may develop due to reasons such as superficial mucosal inflammation of cancer, cancer-related erosion in blood vessels, or vascular involvement. Infections secondary to obstructive lesion may also cause hemoptysis. Squamous cell lung carcinomas are associated with increased hemoptysis.[12,17]

Table 1 Differentiating hemoptysis from pseudohemoptysis[27,28]

	Hemoptysis	Pseudohemoptysis		
Etiology	Cardiorespiratory	Gastrointestinal	Upper respiratory (mouth, nose, throat)	Serratia marcescens
Associated symptoms and findings	Cough, dyspnea, chest pain Anemia is rare	Abdominal pain/tenderness, nau sea/ vomiting, black/tarry stools, history or signs of chronic hepatic disease, chronic nonsteroidal antiinflammatory drug use, heavy alcohol use, history of peptic ulcer disease, anemia frequently associated	Bleeding in oral cavity or nasal fossa (epistaxis, bleeding gums, gingivitis, telangiecta sias, ulcers, varices)	Recent hospitaliza tion, mechanical ventilation, pres ence of invasive device, recent procedure
Characteris tics of blood	Bright red, foamy Alkaline pH	Coffee ground (dark brown/black), mixed with food particles, present in nasogastric aspirate, acidic pH	Bright red Also present in upper respiratory tract	No red blood cells in sputum
Possible diagnostic tests	Chest radiography, computed tomography, computed tomography angiography, bronchoscopy	Esophagogastroduodenoscopy	Nasopharyngoscopy	Positive culture

Cardiovascular events resulting in pulmonary venous hypertension may cause cardiac hemoptysis. The most common cause is systolic cardiac failure due to left ventricular dysfunction. Additionally, severe mitral stenosis and pulmonary embolism are other causes.[13] Hemoptysis may be one of the first symptoms in diffuse alveolar hemorrhage.[18]

Pulmonary arterovenous malformations, peudoaneurysms and aortobronchial fistulas may result in hemoptysis.[6]

In the literature, the frequency of cryptogenic or idiopathic hemoptysis varies between 7-25%. The prognosis for idiopathic hemoptysis is generally good and after 6 months of follow-up, of disappears of these patients.[5]

Iatrogenic hemoptysis may occur due to endoscopic trauma during bronchoscopy, or in patients with thrombocytopenia, or due to the adverse effects of medications.[13]

Menstrual hemoptysis is menstruation-induced hemoptysis due to intrathoracic endometriosis. In these patients, the relationship of hemoptysis with the menstrual cycle and the ability to demonstrate radiological foci of hemoptysis during this period are important for diagnosis.[19] Although hemoptysis is rare in asthma patients, it can sometimes be seen during an attack in COPD patients.[20,21]

The optimal diagnostic approach for life-threatening hemoptysis has not yet been determined. Clinical algorithm (anamnesis, clinical and radiological findings and other further tests) leads to correct diagnosis (Table 2).

Table 2. Causes of hemoptysis[4,6]

System	Disease
Cardiovascular	Aortic aneurysm or bronchovascular fistula
	Arteriovenous malformation
	Congenital heart disease
	Congestive heart failure Mitral stenosis
	Pulmonary embolism/infarct
	Primary pulmonary hypertension
	Pulmonary artery aneurysm
	Ruptured thoracic aneurysm
Infectious	Bronchitis/pneumonia from bacterial and viral illnesses
	Lung abscess
	Mycetoma/invasive pulmonary fungal disease (aspergillosis)
	Necrotizing pneumonia
	Parasites
	Septic embolism
	Tuberculosis/nontuberculous mycobacteria
Neoplastic	Bronchiectasis
	Broncholithiasis
	Cystic fibrosis
	Lymphangioleiomyomatosis
Autoimmune	Anti-glomerular basement membrane disease
	Anti-phospholipid syndrome
	Bechet's disease
	Cryoglobulinemia
	Diffuse alveolar hemorrhage from vasculitis
	Goodpasture syndrome
	Granulomatous with polyangiitis
	Henoch-Schonlein purpura
	Microscopic polyangiitis
	Mixed connective tissue disease
	Rheumatoid arthritis
	Systemic lupus erythematosus
	Systemic sclerosis
Hematologic	Disseminated intravascular coagulation
	Latrogenic coagulopathies (anticoagulants/antiplatelet medications)
	Platelet disease
	Thrombotic thrombocytopenic purpura
Other	Cryptogenic
	Drugs: anticoagulants/antiplatelet, bevacizumab, crack/cocaine, nitrofurantoin
	Foreign body aspiration latrogenic
	Trauma

DIAGNOSIS

Factors such as the presence of symptoms suggestive of infection, recent surgical procedures, administration of anticoagulant or antiplatelet drugs, or a known history of tuberculosis, malignancy, autoimmune condition or chronic lung disease, recent travel, parasitic, inactivity, family history of coagulation disorders, may determine the etiology.[22] Patients with hemoptysis should be monitored for tachycardia, tachypnea, weight loss and hypoxia. Color changes such as cyanosis, telangiectasias, pallor, ecchymosis on the skin and mucosal membranes may be indicators of bleeding. Lymph node examination in the neck, axilla and scalene area is important in terms of malignant diseases. The presence of jugular venous distention, edema, additional sounds and murmurs may be cardiovascularly significant. The presence of a previous history of hemoptysis is important for diagnosis. Hemoptysis that recurs several times a year is important in smokers with chronic bronchitis, COPD, and lung cancer. Environmental factors such as asbestos, arsenic, chromium, nickel, and similar substances are other factors that increase the risk of haemoptysis.[23]

Physical examination is nonspecific in hemoptysis. The history and physical examination should focus on determining the etiology of bleeding. Complete blood count is useful in identifying thrombocytopenia contributing to hemoptysis. Coagulation panel, blood group determination and cross-matching should be performed.[6]

Standard PA chest radiography, thorax computed tomography (thorax CT) and fiberoptic bronchoscopy (FOB) are the most commonly used diagnostic methods. Chest radiography is the first examination method that can be performed quickly, cheaply and easily in patients with hemoptysis. Identifying and localizing the bleeding focus with chest radiography is important in diagnosis. It indicates underlying parenchymal or pleural infection, chronic lung diseases, atelectasis, alveolar hemorrhage, cavitary lesions at the bleeding site. In cases with negative chest radiography, thorax CT and/or bronchoscopy should be evaluated.[8,24,25]

Thorax CT is recommended before bronchoscopic evaluation in patients with hemoptysis.[2] Thorax CT is a noninvasive test that provides information about the lung parenchyma, airways and thoracic vessels in patients with hemoptysis using contrast material. Accuracy varies from 63% to 100% and can indicate underlying causes such as lung cancer, bronchiectasis, respiratory infection.[26]

In angiographic evaluation on thorax CT, the pulmonary arterial system as well as bronchial and non-bronchial arteries should be imaged to identify the bleeding focus, reduce recurrences, and indicate embolizations and endobronchial treatments. With thorax CT, new vascular formations originating from normal or hypertrophic bronchial arteries, aortic branches and intercostal arteries in the mediastinum can be clearly seen.[24,25] Multidetector tomographies can show bronchial and non-bronchial systemic arterial bleeding foci more clearly.[23]

Tomography is better than bronchoscopy in detecting the underlying cause. While the rate of detecting the underlying cause with bronchoscopy is 8%, this rate is around 77% with thorax CT. Despite this, bronchoscopy is an indispensable diagnostic method in endobronchial lesions localized in the distal bronchial structures.[5]

Bronchoscopy is accepted as the primary method, especially in the diagnosis and localization of massive hemoptysis. Bronchoscopy is most useful in detecting endobronchial lesions in diagnosis and treatment.[6] It also evaluates the bronchial mucosa, allows taking samples for tissue pathology and microbial tests, and removing blood and foreign bodies.[27] Fiberoptic bronchoscopy is preferred in patients requiring airway control and in patients with bilateral lung disease.[3] While rigid bronchoscopy is used effectively to control endobronchial bleeding, the possibility of providing bleeding control with the more frequently used FOB is more limited. Rigid bronchoscopy is performed under general anesthesia. It also allows for the removal of blood or foreign objects and shrinkage of the tumor. However, the rigid bronchoscope only reaches the proximal airways unless an additional device is attached. In intensive care, flexible bronchoscopy can be performed at the bedside with sedation instead of anesthesia. If intervention in the respiratory tract is required, intubation should be performed beforehand.[13,28] The best result is the combined use of BT and FOB.[23]

Digital angiography (DSA) is a diagnostic and therapeutic procedure that can provide endovascular treatment in patients with a bleeding focus previously detected by examinations such as CT angiography.[29]

Those with massive hemoptysis, hemodynamic instability, or respiratory distress should be treated in an intensive care unit with access to radiological, endovascular, bronchoscopic, and surgical care.[2,13]

TREATMENT

Hemoptysis has three purposes; It is important to prevent aspiration, stop bleeding, and determine the underlying cause.[23] Patients with respiratory distress should be intubated and remnants of the endobronchial clot should be aspirated immediately. During active bleeding, the lateral decubitus position should be taken on the side where the bleeding occurs, strict bed rest should be ensured, and oral intake should be stopped.[3,26] Patients should be provided with oxygen support and bronchoscopy should be performed within 48 hours at the latest. Bronchoscopy allows identification of the bleeding site, washing the bleeding site with ice or adrenaline serum, buffering the bleeding focus with a balloon, and coagulation with electrocautery, laser and argon plasma in malignant cases.[2,4]

Borderline data are available for antifibrinolytics such as tranexamic acid. However, it can be used to prolong bleeding volume and duration.[4,13]

Endovascular embolization therapies are currently an effective and less invasive method.[30] Endovascular embolization reduces the pressure within fragile hypertrophic vessels, also regulating the preoperative condition.[23] Despite the frequent recurrence rate, BAE is the primary treatment. Bronchial artery embolization, commonly performed as it is often responsible for massive hemoptysis, is an endovascular embolization method that achieves 90% bleeding control.[4-6] Additionally, embolization of non-bronchial systemic arteries or pulmonary arteries should be considered.[4,6] Arterial embolization is the preferred treatment for massive or recurrent hemoptysis and is increasingly being used for non-massive hemoptysis due to its minimally invasive nature.[3,31] The technical success rate of embolization ranges from 81% to 100%. However, the likelihood of failure is higher in the presence of extrabronchial systemic collaterals and bronchopulmonary shunts. If there is no pathology in the bronchial circulation, non-bronchial systemic and pulmonary vessels can be considered.[4]

If the cause of hemoptysis is thoracic trauma or iatrogenic pulmonary vascular trauma, surgical treatment is the primary option.[6,31] Surgical intervention is the definitive treatment in cases of hemoptysis resistant to other options, where the source of bleeding is unilateral and well localized, lung reserve is sufficient, or after the patient is stabilized.[28] Surgical procedures may include pneumonectomy, lobectomy, segmentectomy, wedge resection, thoracoplasty, cavernostomy, bronchial artery ligation, and devascularization. Surgery has a high mortality risk (2-18%), and due to the high risk of complications such as perioperative bleeding, asphyxia, bronchopleural fistula, respiratory failure, this rate can increase up to 25-50% in active bleeding and emergency situations (Figure 2, 3).[28]

CONCLUSION

Haemoptysis is a significant pulmonary symptom that can arise from various aetiologies. More than half of the cases presenting with complaints of haemoptysis at secondary healthcare facilities are comprised of infectious causes and idiopathic haemoptysis. The advancement of preventive medicine today, along with progress in diagnosis and treatment, leads to changes in the frequency of diseases in haemoptysis aetiology and highlights haemoptysis associated with more prominent diseases. Patients with haemoptysis should be evaluated together by pulmonology, thoracic surgery, and interventional radiology based on the severity.

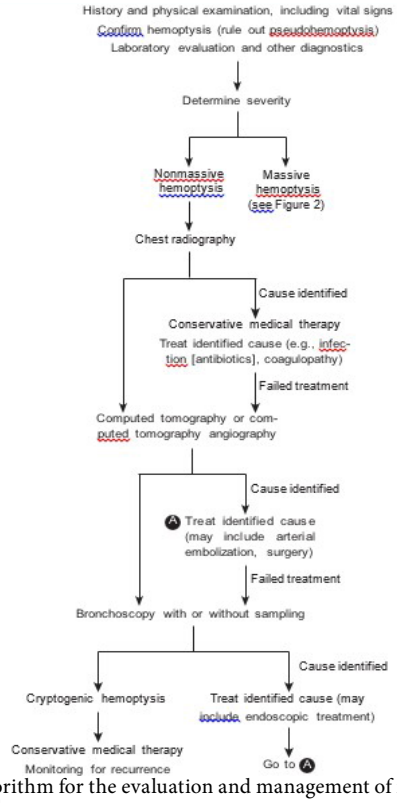

Figure 2. Algorithm for the evaluation and management of nonmassive hemoptysis[22,31]

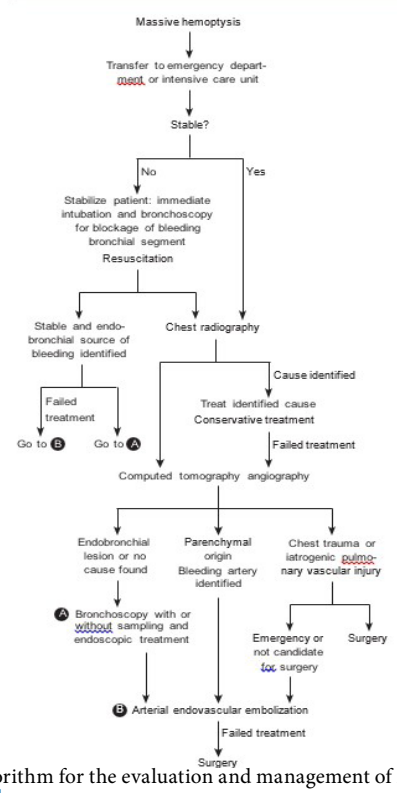

Figure 3. Algorithm for the evaluation and management of massive hemoptysis[22,31]

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclwosure

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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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Review

Acute phase reactants

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ABSTRACT

The serum concentrations of certain proteins are altered in various conditions such as infection, trauma, inflammatory arthritis, malignancy, autoimmune and systemic inflammatory diseases. These proteins are known as positive or negative acute phase reactants. While albumin and transferrin belong to the negative acute phase reactants, alpha-1-acid glycoprotein, alpha-1-antitrypsin, alpha-2-macroglobulin, C-reactive protein, ceruloplasmin, haptoglobin, serum amyloid A and fibrinogen are known as positive acute phase reactants. This review discusses the clinical use of C-reactive protein, erythrocyte sedimentation rate and procalcitonin.

Keywords: Acute phase reactants, CRP, ESR, procalcitonin

INTRODUCTION

In response to infection, trauma and inflammation, changes (increases or decreases) occur in the blood levels of certain proteins in many organisms, including humans. Among these proteins, the levels of albumin and transferrin decrease under conditions such as infection, trauma and inflammation, whereas the levels of alpha-1-acid glycoprotein, alpha-1-antitrypsin, alpha-2-macroglobulin, C-reactive protein (CRP), ceruloplasmin, haptoglobin, serum amyloid A and fibrinogen increase.[1] Because of the association of these serum protein increases with inflammatory conditions, they are also referred to as acute phase reactants (APR).[2]

This review discusses the clinical use of CRP, which is the most commonly used APR in practice, erythrocyte sedimentation rate (ESR), an indirect measure of the acute phase response and in particular fibrinogen levels, and procalcitonin, which is more specific to infection.

C-REACTIVE PROTEIN (CRP)

CRP is one of the most important members of the APR family. CRP has been detected in every organism studied, including arthropods, with structural differences between species. Human CRP is a pentameric protein with a molecular weight of approximately 23 kDa, consisting of 206 amino acid residues and five non-covalently bound identical subunits.[3] Human C-reactive protein was first identified as a plasma protein that precipitates the C-polysaccharide (PnC) from the cell wall of *Streptococcus pneumoniae*.[4]

Synthesis

CRP gene expression occurs in hepatocytes in the liver in response to elevated levels of inflammatory cytokines, primarily interleukin-6 (IL-6). In addition to the liver, CRP is also synthesised by smooth muscle cells, macrophages, endothelial cells, lymphocytes and adipocytes. Many factors can alter baseline CRP levels, including age, gender, smoking, weight, blood lipid levels and blood pressure.[5] The pentameric form of native CRP (nCRP) can irreversibly dissociate into free subunits known as monomeric CRP (mCRP) under certain conditions.[6] The normal range of CRP can vary widely between laboratories. Therefore, a reported high level can sometimes be misleading. A CRP level of >1 mg/dL (10 mg/L) indicates clinically significant inflammation, while levels between 0.3 and 1 mg/dL (3 to 10 mg/L) generally indicate low-grade inflammation.[7] The half-life of CRP is approximately 19 hours under both physiological and pathological conditions.[8]

Inflammation and CRP

CRP is universally recognised as a marker of acute inflammation. However, it has also been shown that CRP is an active participant in the inflammatory process and not just a marker of inflammation. Therefore, CRP exhibits both pro-inflammatory and anti-inflammatory effects.[9] CRP assists in the recognition and elimination of pathogens and enhances the clearance of necrotic and apoptotic cells.[10] Under physiological conditions, stable nCRP gains specificity for binding to proteins such as factor H, oxidised LDL and complement C3b in the acidic environment of inflamed

tissue. Binding of circulating nCRP to membrane lipids on the surface of activated platelets and apoptotic cells leads to subunit dissociation into the mCRP form. This form of CRP induces potent pro-inflammatory activities such as secretion of IL-8 by neutrophils and human coronary endothelial cells, adhesion of neutrophils to platelets and endothelial cells, delay of neutrophil apoptosis and release of neutrophil extracellular traps.[11]

Infection and CRP

CRP has long been used as a sensitive marker to determine the presence and severity of infection and to monitor the efficacy of treatment.[1] During infection, CRP increases in response to the elevation of inflammatory cytokines, particularly IL-1 and IL-6. The interaction of CRP with the immune response to microorganisms is thought to be primarily through the classical complement pathway.[5] CRP was originally identified as a plasma protein that precipitates the C-polysaccharide from the cell wall of S. pneumoniae.[4] A study in mice showed that CRP contributes to the clearance of intravenously injected bacteria from the blood and reduces early dissemination of infection to the liver and spleen.[12] Another study reported that CRP levels are higher in systemic infections compared to local infections and colonisation, but CRP levels alone could not differentiate between different types of infection.[13]

ERYTHROCYTE SEDIMENTATION RATE (ESR)

The ESR is defined as the rate (mm/hour) at which erythrocytes settle in the plasma in a given time in anticoagulated blood.[14] Essentially, the ESR is an indirect indicator of the acute phase response and primarily acute phase proteins, particularly fibrinogen.[15] This phenomenon was first observed in 1897 by Dr Edmund Faustyn Biernacki, who noticed that red blood cells sediment more quickly in the presence of high levels of fibrinogen.[16] Many factors, including acute tissue injury, soft tissue infection, rheumatic disease, malignancy and physiological conditions such as pregnancy, can cause an increase in ESR.[17] Because the erythrocyte sedimentation rate can be influenced by several factors (inflammation, trauma, infection, morphological changes in erythrocytes, anaemia, polycythemia), it is difficult to establish a normal limit or reference range. It is generally defined as age (years)/2 for males and age (years)+10 for females.[18]

Clinical Use

Unlike other acute phase reactants, ESR does not increase very rapidly at the onset of inflammation and returns to normal levels more slowly after the inflammation subsides. This should be taken into account in clinical assessment. ESR begins to rise approximately 24-48 hours after the onset of inflammation and may take weeks to return to normal levels as inflammation resolves.[19] Although ESR has low sensitivity and specificity as an acute phase reactant, an ESR greater than 100 mm/hour indicates significant underlying inflammation.[14] In a large study of patients with an ESR greater than 100 mm/hour, 40% had infections (most commonly pneumonia), 38% had underlying rheumatic disease (most commonly rheumatoid arthritis), and 36% had malignancy.[20] In a retrospective study of 1006 patients, infections (33%) were the most common cause of ESR values above 100 mm/hour, while malignancies (17%) and inflammatory diseases (14%) were reported less frequently.[21]

PROCALCITONIN (PCT)

Procalcitonin is a prohormone composed of 116 amino acids that acts as a precursor to calcitonin and is synthesised during bacterial infections.[22]

Synthesis

Under normal conditions, PCT is synthesised in thyroid C-cells from the CALC-1 gene located on chromosome 11. This mRNA product is subsequently cleaved into three different molecules: active calcitonin (32 amino acids), katacalcin (21 amino acids) and N-terminal procalcitonin (57 amino acids).[23] In healthy individuals, all PCT synthesised by thyroid C-cells is converted to calcitonin, resulting in very low circulating levels (≤0.1 ng/ml).[22] In the presence of a pro-inflammatory stimulus, particularly of bacterial origin, PCT is secreted not only by thyroid C-cells but also by neuroendocrine cells in the gut and lungs.[24]

Infection and PCT

The relationship between procalcitonin and bacterial infections was first described in 1993, when a calcitonin-like immunoreactivity was detected at higher levels in the blood of patients with infections compared with those without signs of infection. This study showed that procalcitonin concentrations correlate with the severity of infection, increasing up to 2000-fold in patients with septic shock and decreasing rapidly with antibiotic treatment.[25] Following this study, it was suggested that procalcitonin may be more specific for infection than other acute phase reactants, prompting numerous studies.[26] According to a meta-analysis published in 2011, procalcitonin could reduce antibiotic use without increasing mortality in patients with respiratory infections and sepsis, and could be used to guide treatment.[27] Another study reported that procalcitonin is useful in diagnosing patients presenting to the emergency department with pneumonia versus heart failure and serves as an indicator of one-year mortality.[28]

Procalcitonin synthesis is activated by microbial toxins, interleukin-1, interleukin-6 and tumour necrosis factor-α, whereas it is inhibited by interferon-γ released by viruses.[29,30] An in vitro study found that procalcitonin induces human monocyte chemotaxis at concentrations present in the circulation during bacterial infections.[22] Because of its elevation during bacterial but not viral infections, the US Food and Drug Administration (FDA) has approved procalcitonin for use in initiating and determining the duration of antibiotic therapy for lower respiratory tract infections.[31] However, recommendations for the use of procalcitonin in the diagnosis of bacterial co-infections vary.[32] A study in influenza patients found that procalcitonin had a negative predictive value of 94%, making low PCT levels an effective biomarker for excluding bacterial co-infection, especially in patients without septic shock.[33] However, a study of hospitalised COVID-19 patients suggested that procalcitonin is not useful for the diagnosis of bacterial co-infection.[34] In a study of patients with Crimean-Congo haemorrhagic fever (CCHF), despite the viral nature of the infection, procalcitonin levels were higher in patients with severe clinical presentation, suggesting that procalcitonin levels in the first two days of illness may predict mortality.[35]

CONCLUSION

Acute phase reactants may increase or decrease as indicators of inflammation due to various causes such as infections, rheumatic diseases, trauma and malignancy. However, none of these alone is sufficient to diagnose a disease. In particular, acute phase reactants such as ESR and CRP, which are influenced by physiological conditions such as age, gender and race, should be evaluated in conjunction with the patient's clinical presentation.

ETHICAL DECLARATIONS

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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