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TURKISH JOURNAL OF INTERNAL MEDICINE

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Original Article

Examination of the Theses Published in Family Medicine Related to Health Literacy With Social Network Analysis

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ABSTRACT

Background In recent years, it has been seen that the concept of health literacy has an increasing interest in academic studies and theses published in Turkey. Within the scope of the study, the theses written on health literacy in the field of family medicine were evaluated. It was aimed to reveal the thematic development and knowledge structure of the theses published in this field.

Material and Methods Within the scope of this study, social network analysis was carried out based on the keywords obtained from the theses prepared with the target of health literacy. Theses included in the study were accessed via https://tez.yok.gov.tr/UlusalTezMerkezi/. The studies that include the phrase "health literacy" in the title were selected in the examination scope, and the keywords obtained from these theses were listed.

Results It is observed that the concept with the highest degree of centrality and betweenness centrality is "health literacy," as expected. Following the keyword "health literacy," the keywords "life quality," "mortality," "family medicine," "vaccine," and "diabetes mellitus" have the highest degree of centrality, respectively. It is observed that the betweenness centrality values of the "newest vital sign" and "life quality" keywords are quite high compared to the degree centrality values.

Conclusions Through this study, researchers can focus on issues that are not emphasized much, create original research questions and contribute to the literature. In addition, it may be important to reveal which concepts are associated with the concept of health literacy through this study.

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Introduction

Health literacy has been defined by the World Health Organization (WHO) as "a set of cognitive and social skills that encourage individuals to access, understand and use the information to maintain and improve their good health and determine their abilities in these matters."[1] According to the working definition developed by the Health Literacy Europe (HLS-EU) Consortium, health literacy is related to general literacy and accessing, understanding, evaluating, and applying health information to make decisions and make judgments in daily life related to health care, disease prevention, and health promotion to maintain or improve quality of life throughout life. It has a scope and framework that requires people's knowledge, motivation, and competencies.[2]

Because all individuals need health services, it would not be wrong to say that everyone is a health user. The health sector has a very complex structure due to the constant changes in technology and information. In this complex structure, the individual's health status is in question, and therefore, it is impossible not to have any knowledge or equipment. When it comes to the individual's level of health knowledge, the concept of health literacy appears. At this very point, the importance of the patient's ability to understand and interpret the medical information given to them and make decisions accordingly comes to the fore.

In the European Health Literacy study covering eight European Union member countries, it was determined that the health literacy level of the participants was inadequate at 12.4%, problematic at 35.2%, sufficient at 36%, and excellent at 16.5%. According to the national adult literacy study in the USA, 12% adequate, 53% medium level, 22% basic level, 14% below the basic level of health literacy were found.[3] In the study conducted in 2019, it was reported that 57.9% of the participants were found to have insufficient health literacy levels.[4]

In recent years, it has been seen that the concept of health literacy has an increasing interest in academic studies and theses published in Turkey. Within the scope of the study, the theses written on health literacy in the field of family medicine were evaluated, and it was aimed to reveal the thematic development and knowledge structure of the theses published in this field. Thus, the present study aims to give an idea about the trend in the literature on family medicine studies that will work on health literacy in the future, create a research question, and guide them.

Material and Methods

Within the scope of this study, which was evaluated with a bibliometric method, social network analysis was carried out based on the keywords obtained from the theses prepared with the target of health literacy. Theses included in the study were accessed via https://tez.yok.gov.tr/UlusalTezMerkezi/. The studies that include the phrase "health literacy" in the title were selected in the examination scope, and the keywords obtained from these theses were listed. As a result, 39 theses and 75 keywords obtained from these theses were included in the study. The bibliometric analysis comprises obtaining and analyzing data about a specific topic or range of issues. The bibliometric method applies mathematical and statistical methods to written communication tools such as books, journals, and articles.[5] By examining the articles and scientific papers in the literature with the bibliometric approach, the relationships between the documents can be statistically analyzed; and a general inference can be made about the relevant literature, and it can be determined how the articles have developed over time or the trend towards on the relevant topics.[6] Social network analysis (SNA) is a statistical method that can be widely used in interdisciplinary fields to analyze bibliometric studies in recent years.[7] SNA enables the examination and analysis of social networks. Social networks are structures that show the relations and ties between the units or actors interacting.[8] Within the scope of this study, the units are the keywords collected from the theses on health literacy in family medicine. Relationships and bonds between keywords are tried to be revealed and visualized. There are specific criteria used in social network analysis to indicate these relationships. SNA enables the review and analysis of social networks. Social networks are structures that show the relationships and links between units or actors interacting with

each other. For this study, units are the keywords taken from theses on health literacy in family medicine. SNA tries to reveal and visualize the relationships and links between keywords. There are specific criteria used in SNA to indicate these relationships. With social network analysis network map of keywords is visualized.

The centrality criterion is one of the essential criteria used in the SNA. In studies, centrality criteria can be used in two different ways as degree and betweenness centrality. With degree centrality, the sum of the connection numbers of the actors in the network with other actors is calculated. Actors with a high degree of centrality are in the most central position in the network.[8] A higher degree of centrality indicates a more central keyword; therefore, it can be interpreted as a common keyword that has been actively studied in the literature.[9] If it is considered within the scope of the study, keywords with a high degree of centrality have more ties with other keywords and are in a central position in the network map. Betweenness centrality indicates the degree to which an actor is between two unrelated actors. An actor with a high centrality betweenness establishes a connection and mediates between two actors that are not connected (Wasserman and Faust, 1994:188). Within the scope of the study, the keywords obtained from 39 theses related to health literacy were examined by SNA, and the network map created by these keywords was tried to be revealed. Analyzes were performed in the UCINET[10] program. A 75 x 75 data matrix was prepared in the UCINET 6 program with 75 keywords obtained from the theses. It has been determined that different expressions are used for the concept of health literacy in some theses. These expressions were entered into the data matrix as a single keyword so that these expressions with the same meaning are not included in the matrix separately.

Results

The cumulative distribution of theses published on health literacy in family medicine between 2016 and 2021 is given in Figure 1. When Figure 1 is examined, it is understood that the date when theses on health literacy in family medicine started to be written as 2016. There has been a noticeable increase in the number of theses since then. It is aimed to reveal the network structure of the keywords obtained from 39 theses by using SNA.

For this purpose, 75 keywords of 39 theses related to health literacy were processed into a

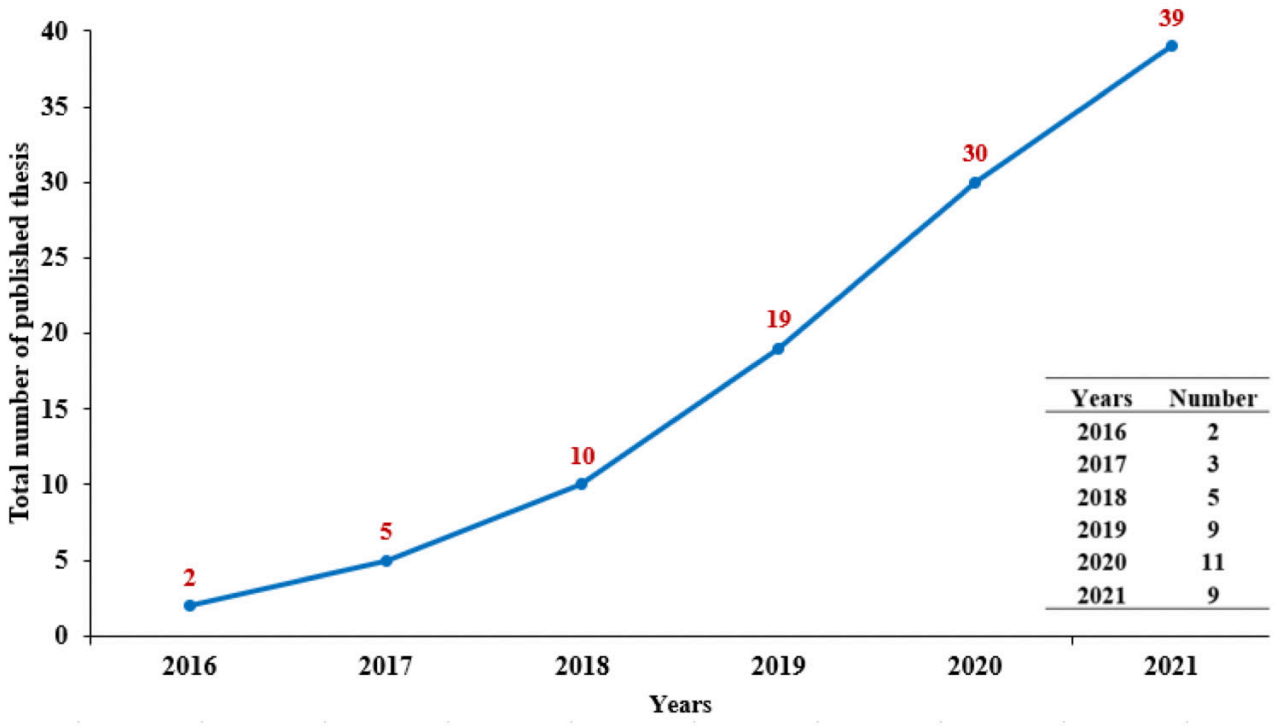

Figure 1. Distribution of the thesis according to the years.

75x75 data matrix and subjected to social network analysis. The degree and betweenness centrality findings regarding the keywords are given in Table 1. To avoid making the table too long, keywords with a degree centrality of less than six were not included.

When Table 1 is examined, it is observed that the concept with the highest degree of centrality and betweenness centrality is "health literacy," as expected. Following the keyword "health literacy," the keywords "life quality," "mortality," "family medicine," "vaccine," and "diabetes mellitus" have the highest degree of centrality, respectively. These keywords are the concepts with the highest number of links, the most focused on the network, and discussed in many theses. The concepts of "health literacy," "newest vital sign," and "life quality" have a high betweenness centrality. Keywords with high betweenness centrality connect concepts that are not related to each other by acting as a bridge. It is observed that the betweenness centrality values of the "Newest vital sign" and "life quality" keywords are quite high compared to the degree centrality values. Although the newest vital sign keyword is not used frequently in theses, it can be said that it brings together concepts that are not related to each other at a high rate. The network map of the keywords obtained from the theses written on health literacy in family medicine in the literature is given in Figure 2.

Discussion

In today's world, which is accepted as the information age, individuals are expected to recognize and identify their diseases and make decisions they think are suitable for their health. The ability to take these decisions correctly is related to the level of health literacy.[11]

Health literacy, which is included in the scope of health promotion, changes the lifestyle and living conditions of the individual, enabling him to acquire the level of knowledge, individual skills, and self-confidence that will lead him to behavior that will improve both individual and public health.[12] It supports and develops the ability of the individual to reach the correct information and service and the ability to use this service to protect and maintain health.[13] Thus, it strengthens the more effective use of existing health services, creating quality conditions in health services and the individual's competence over his health and public health.[14,15] It has been shown that limited or inadequate health literacy is associated with poor health decisions, more risky health behaviors, worse health parameters, and increased use of the health system.

As the concept of health literacy has become popular in recent years, it is seen that a substantial number of studies are published every year in the field of medicine, taking this concept to the center.

Table 1. Top keywords with degree centrality and betweenness value for health literacy.

Degree centrality		Betweeness centrality	
Keyword	Value	Keyword	Value
Health literacy	72	Health literacy	2,528.50
Life quality	12	Newest vital sing	144
Mortality	9	Life quality	21
Family medicine	7	Mortality	8
Vaccine	7	Family medicine	6.50
Diabetes mellitus	7	Diabetes mellitus	5.50
Chronic disease	6	Vaccine	4.50
Primary health care	6	Primary health care	4
Hypertension	6	Chronic disease	3.83
Caregiver	6	Periodical examination	3
Periodical examination	6	Hypertension	2.67

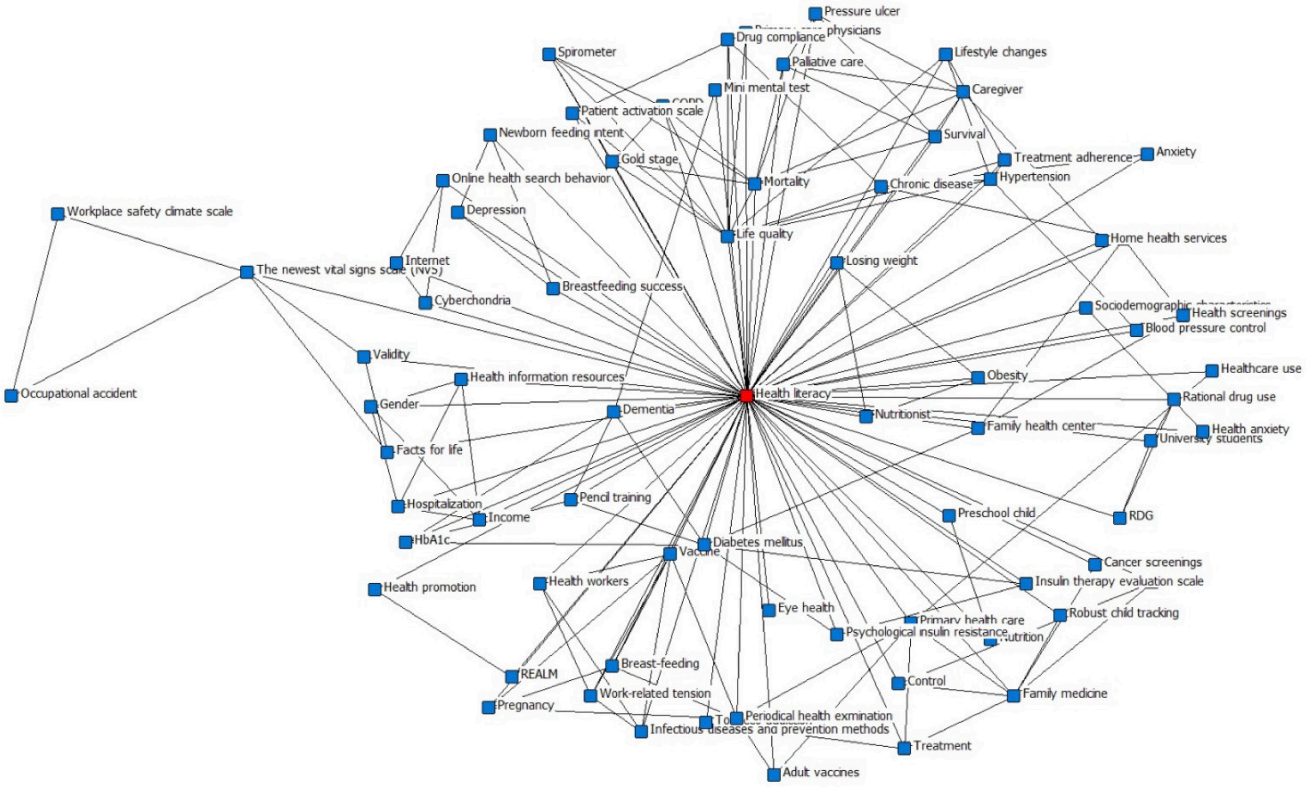

Figure 2. Network map of keywords obtained from theses included in the study.

The present study aims to create a network map of the keywords obtained from the theses published in family medicine related to health literacy.

As a result of the findings obtained by social network analysis, the concept with the highest degree of centrality is the phenomenon of health literacy. This finding is expected, as this study focused on the theses on health literacy, and the keyword health literacy was searched for in every thesis. After the "health literacy" case, the degree centrality of the "life quality" and "mortality" cases was observed to be high. The concept of health literacy has often been studied together with "life quality" and "mortality." Quality of life refers to a person's subjective assessment of their well-being and ability to perform physical, psychological, and social functions.[16] Quality of life is used primarily in the assessment of health status and health resources. It is used as an aspect of influencing factors and health promotion measures with higher stability and sensitivity.[17] Although it has been shown in the literature that there is a positive relationship between quality of life and health literacy, it has been stated that individuals with low health literacy levels cannot pay much attention to their health issues. As a result, they may adopt harmful habits that may adversely affect their quality of life.[15,18] For this reason, it is thought that the theses included in the study were conducted to examine the relationship between health literacy level and quality of life and determine how they affect each other. Another concept that was mainly studied about health literacy was determined as mortality. Although there is a meta-analysis study[19] showing that health literacy is associated with mortality and the quality of life, inadequate health literacy may lead to reduced quality of life due to inadequate and wrong decisions about one's health and even death.

Other findings obtained by social network analysis are the findings related to betweenness centrality. Within the scope of the study, the case with the highest centrality is "health literacy." In other words, it acts as a bridge between concepts that are not related to each other. Since health literacy occurs in every thesis reviewed, it is not surprising that betweenness centrality is highest. It is observed that the concepts of "newest vital sign" and "quality of life" have a high centrality in between, following the phenomenon of health literacy. Based on this finding, it can be said that

these cases were handled together with cases that were not related to each other in different theses. In other words, these cases were not studied together with the same cases. The Newest Vital Sign scale consists of 6 questions and measures an individual's reading and understanding of a food label. It is advantageous because it measures calculation, reading, and comprehension aspects and has 3-6 minutes of application time. In the theses examined, different concepts were tried to be brought together, and their relations with health literacy were tried to be revealed by using this measurement tool.

Conclusions

This study is a guide for researchers who want to work on health literacy in family medicine to show which subjects the concept of health literacy, which has gained popularity in recent years, is intensely associated with. Through this study, researchers can focus on issues that are not emphasized much, create original research questions and contribute to the literature. In addition, it may be important to reveal which concepts are associated with the concept of health literacy through this study.

Conflict of interest

Author declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Study Conception, Data Collection and/or Processing, Materials, Literature Review, Manuscript Preparation held by GO.

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Original Article

Evaluation of Gastric Polyps: A Single-Center Study Conducted in Turkey's Southeast Anatolia Region

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ABSTRACT

Background Gastric polyps are often detected incidentally during endoscopic procedures performed for different reasons and may sometimes manifest by gastric bleeding, pyloric stenosis, iron deficiency anemia and abdominal pain. Our study aimed to investigate the demographic data of the cases found to have gastric polyps at the gastroenterology endoscopy unit, histologic type of the polyps, their localization and size, and their relationship with *Helicobacter pylori.*

Material and Methods Between September 2016 - September 2019, gastric polyps were detected in 255 of 9,771 cases who underwent upper gastrointestinal system endoscopy at the Gastroenterology Endoscopy Unit of our hospital. Demographic data, endoscopy reports and pathology results of these patients were retrospectively reviewed from the hospital registry system.

Results Of 255 cases included in the study, 160 (62.7%) were female, and 95 (37.3%) were male, with a mean age of 56.9 (min: 19, max: 95). A total of 336 polyps were detected in 255 cases, with 1.3 polyps per case. 36 (10.7%) of gastric polyps were found to be fundic gland polyps, 32 (9.5%) were found to be foveolar hyperplasia, 137 (40.8%) were found to be hyperplastic polyps, 5 (1.5%) were found to be xanthomas, and 6 (1.8%) were found to be neuroendocrine tumors.

Conclusions According to this study, 90% of gastric polyps detected endoscopically in southeast Turkey are smaller than 5 mm and located most commonly in the corpus; the most common histologic subtype is hyperplastic polyps.

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Introduction

Gastric polyps are usually asymptomatic mucosal protrusions originating from the gastric mucosa or submucosa and extending into the lumen. Gastric polyps are detected incidentally during endoscopic procedures performed for different reasons. Sometimes they can cause gastric bleeding, pyloric stenosis, iron deficiency anemia and abdominal pain.[1] The frequency of gastric polyps in the general population varies between 0.3% and 6%.[2,3] Hyperplastic polyps (HPs) and fundic gland polyps (FGPs) constitute most polyps classified according to their histopathological features, and adenomatous polyps comprise a small portion.[2] HPs are associated with *Helicobacter pylori* (HP) infection, while FGPs are related to the use of proton pump inhibitors.[3] While HPs decrease in western society due to the decline in the frequency of HP, there is an increase in FGPs. However, HPs are the most common polyps in Asian countries where HP infection is common.[4] Histopathological evaluation should be performed by biopsy, especially for adenomatous polyps, as gastric polyps may be associated with familial polyposis syndromes and can potentially be premalignant or malignant lesions.[5] Due to the malignant potential of gastric polyps, their diagnosis and follow-up gain importance.

This study aims to investigate the frequency of polyps detected during gastroscopy procedures in our hospital, demographic characteristics of the cases with polyps, histopathological features, localization, size and number of polyps and their relationship with HP infection.

Material and Methods

We detected gastric polyps in 299 of 9,771 patients who underwent upper gastrointestinal system endoscopy between September 2016 and September 2019 at the Gastroenterology Endoscopy Unit of our hospital. We retrospectively reviewed these patients' demographic data, endoscopy reports, and pathology results from the hospital registry system. Since our study was retrospective, informed consent was not obtained from the patients. The ethics committee of our hospital approved this study.

Some patients underwent multiple procedures, and 44 of the 299 patients studied had polyps. Together with the data of 255 patients, we evaluated only the first endoscopy and pathological findings of these 44 patients. We recorded the total number, size, anatomical localization, histopathological features and presence of HP in all patients and divided the polyps into groups according to their localization as gastric cardia, fundus, corpus, antrum and multiple regions. We considered the size of the giant polyp to be determinant in patients with various polyps of different sizes. All gastroscopy procedures were performed with 10% lidocaine spray (xylocaine 10% spray; Astra Zeneca, Sweden) under topical pharyngeal anaesthesia. All patients gave written informed consent before the procedure. Polypectomy was performed on all polyps except those that could not be removed due to anatomical localization or anticoagulant use. Small polyps (<5 mm) were removed with forceps and large polyps (>5 mm) with a snare. We classified polyps according to the modified classification of the World Health Organization (WHO). We excluded patients with gastric tumour and subepithelial lesions and a history of gastric surgery.

Statistical Analyses

Statistical analysis was performed using SPSS 16.0 (Chicago, USA) program. While the arithmetic means±SD, minimum and maximum values were used to define numerical data, categorical data were expressed as percentages (%). Kolmogorov-Smirnov test was used to determine the normality of data. Independent T-test was used for normally distributed numerical data, and chi-square test was used to test the differences between the categorical subgroups. A p-value of <0.05 was considered statistically significant.

Results

A total of 255 cases with gastric polyps were included in the study. 160 (62.7%) of these cases were female, 95 (37.3%) were male, and the mean age was 56.9 (min: 19, max: 95). A total of 336 polyps were detected in 255 cases, with 1.3 polyps per case. Histopathological features, size, localization and number of polyps were

Table 1. Number, size, localization and histopathological features of stomach polypoid lesions.

	Localization of polyps					Size of polyps			Number of cases	
Histopathological type of polyps	Cardia	Fundus	Corpus	Antrum	Total (%)	<5 mm n (%)	5-10 mm n (%)	≥10 mm n (%)	Single polyp	Multiple polyps
Fundic gland polyp	7	17	11	1	36 (10.7)	21 (95.5)	1 (5.6)	0	7	17
Foveolar hyperplasia	12	11	5	4	32 (9.5)	18 (100)	0	0	7	15
Gastritis/stomach mucosa	32	24	38	21	115 (34.2)	90 (95.7)	4 (4.3)	0	66	36
Hyperplastic polyp	37	32	45	23	137 (40.8)	87 (81.3)	12 (11.2)	8 (7.5)	68	41
Xanthoma	1	1	1	2	5 (1.5)	5 (100)	0	0	4	1
Neuroendocrine tumor	1	0	5	0	6 (1.8)	5 (100)	0	0	1	5
Polyps with nobiopsy	1	2	2	0	5 (1.5)	5 (100)	0	0	4	1
Total	91	87	107	51	336	230 (90.2)	17 (6.7)	8 (3.1)		

given in Table 1. Single polyp was detected in 157 cases (61.5%), while more than one polyp was detected in 98 cases (38.5%). The mean age was 56.3±17.4 years in the patients who had a single polyp and 57.7±12.4 years in the patients who had more than one polyp (p=0.449). Considering the size of the largest polyp, it was smaller than 5 mm in 230 cases (90.2%), between 6-10 mm in 17 cases (6.7%) and 10 mm and above in 8 cases (3.1%). Polyps were detected only in the cardia in 58 (23%) cases, only in the fundus in 41 (16%) cases, only in the corpus in 66 (26%) cases, only in the antrum in 41 (16%) cases and in multiple anatomical regions in 49 (19%) cases. Totally, the polyps were detected mostly in the cardia (31.9%). Histopathological evaluation of the lesions which were endoscopically considered polyp in 102 (40%) cases revealed gastritis or normal gastric mucosa. 36 (10.7%) of gastric polyps were found to be FGPs, 32 (9.5%) were found to be foveolar hyperplasia, 137 (40.8%) were found to be HPs, 5 (1.5%) were found to be xanthomas, and 6 (1.8%) were found to be neuroendocrine tumors. More than one histologic type was detected in 18 cases. Since polypectomy could not be performed, five (1.5%) cases did not have pathological examination. Considering the frequency of polyps by age, polyps were detected in a total of 38 cases in the age range of 19-40 years with more than one polyp in 7 of them, in a total of 109 cases in the age range of 41-60 years with more than one polyp in 51 of them and in a total of 108 cases aged above 60 years with more than one polyp in 40 of them *(Figure 1)*. The relationship of polyps with age, gender and HP according to histopathological features was given in Table 2. HP was studied in 195 of the patients included in the study, and it was found to be negative in 54 cases (27.7%) and positive in 141 cases (72.3%). No statistical significance was found between the histopathology of gastric polyps and HP positivity.

Discussion

Gastric polyps are generally asymptomatic and detected incidentally in endoscopic procedures performed for any reason. In our study, polyps were seen in a total of 255 patients among 9,771 gastroscopy procedures performed at the gastroenterology endoscopy unit. The frequency of gastric polyps has been reported to range between 0.3% and 6% in the literature.[2,3,6] This rate has been reported to be 1.2%[7], 2.2%[5] and 1.86%[8] in the studies conducted in different regions of Turkey. In this study conducted in our hospital which admits patients from Turkey's Southeastern Anatolia Region, the frequency of gastric polyps was 2.6%. This rate is consistent with the world data, while slightly higher than studies conducted in Turkey. In a study of 269 patients with polypoid lesions, the average age of the patients

Table 2. Relationship of polyps with age, gender, HP, intestinal metaplasia according to histopathological features.

	Age mean±SD (min-max)	Gender n (%)			Helicobacter pylori n (%)			Intestinal metaplasia n (%)		
Histopathological type of polyps		Female	Male	p value	Negative	Positive	p value	Negative	Positive	p value
Fundic gland polyp	58.95±11.261 (33-78)	15 (68.2)	7 (31.8)	0.523	6 (42.9)	8 (57.1)	0.533	22 (100)	0 (0)	0.059
Foveolar hyperplasia	59.94±13.383 (37-80)	8 (44.4)	10 (55.6)	0.127	5 (38.5)	8 (61.5)	0.309	16 (88.9)	2 (11.1)	0.933
Hyperplastic polyp	59.25±16.203 (21-95)	71 (67)	35 (33)	0.228	20 (26)	57 (74)	0.719	89 (84)	17 (16)	1.000
Xanthoma	59.25±14.385 (38-69)	3 (60)	2 (40)	0.616	2 (66.7)	1 (33.3)	0.658	4 (80)	1 (20)	1.000
Neuroendocrine tumor	63±16.529 (40-75)	5 (83.3)	1 (16.7)	0.530	1 (25)	3 (75)	1.000	3 (50)	3 (50)	0.069
Gastritis/stomach mucosa	52.83±16.219 (19-86)	56 (60.2)	37 (39.8)	1.000	20 (23.8)	64 (76.2)	0.111	77 (82.8)	16 (17.2)	0.500

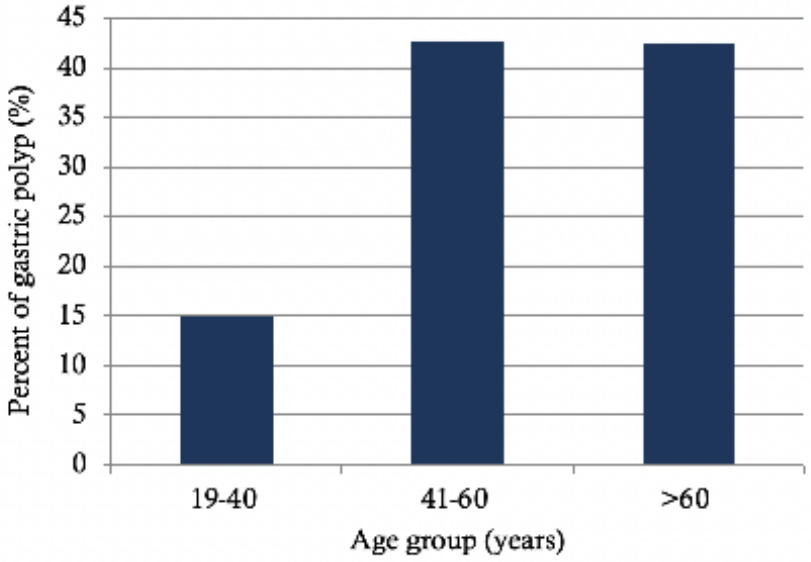

Figure 1. Frequency of gastric polyps according to age ranges.

was 65, and the rate of women was 61%.[9] In another study conducted by Atalay et al.[7], the average age of patients with polyps was 58.4 years, and the rate of women was 67.2%. In our study, the average age of the patients was 56.8, and the rate in women was 62.7%.

Histopathological examination reveals gastritis or normal mucosa rather than polyp in approximately 16-37.5% of the lesions considered polyp endoscopically.[9] In our study, histopathological examination revealed gastritis or normal mucosa in 40% of the lesions that were endoscopically considered polyp. 95.7% of these lesions were polypoid lesions smaller than 5 mm.

Gastric polyps can develop anywhere on the gastric mucosa. Li et al.[10] reported that the most common site for gastric polyps was the antrum, and it constituted 40.7% of all gastric polyps. Another study reported that the most common localization of polyps was the antrum, followed by the corpus.[6] A study conducted in China

reported that the frequency of polyps in the antrum decreased, and the frequency of polyps in the corpus increased.[11] Polyps were also found most commonly in the corpus, with a rate of 31.9% in our study supporting this study. The corpus was followed by the cardia, fundus and antrum, respectively, in polyp frequency. The higher number of polyps in the cardia and fundus than the antrum is associated with FGPs, which are seen in the proximal part of the stomach and tend to be multiple.

Archimandritis et al.[12] reported that most of the polyps (61.9%) were smaller than 5 mm in their study. In another study, 97.2% of all polyps were reported to be smaller than 10 mm.[13] The size of the largest polyp in our study was found to be smaller than 5 mm at a rate of 90.2%, between 6-10 mm at a rate of 6.7% and 10 mm and above at a rate of 3.1%; these findings are compatible with the literature.

HPs are the most common type of gastric polyps.[5] Focal inflammatory reactions and mucosal damage are blamed for the etiology of this type, and these polyps are associated with HP infection and atrophic gastritis.[14] HPs are more common in middle and advanced age individuals, and there was no gender difference.[15] Their incidence in the stomach differ among studies and vary between 18.2% and 76%.[13] Although HPs are considered as benign, these polyps may show dysplastic and malign transformation. Dysplastic foci can be observed in 1-20% of HPs. However, the overall prevalence of dysplasia is 2% in HPs. Only %0.5-8.6 of all HPs are malignant.[5,7] In our study, the mean age of occurrence of HPs was 59.2 years, while 67% in female patients, 40.8% of all gastric polyps were HP and 81.3% were smaller than 5 mm. Eight of HPs (7.5%) were larger than 10 mm, and the polyp size was found to be larger than 10 mm only in HPs in the patients included in the study. In our study, HP was studied in 77 cases diagnosed with HPs, and positivity was detected in 57 cases (74%). However, the high HP positivity was not statistically significant.

FGPs are the most common type of gastric polyps in developed countries, often seen in the proximal stomach.[16] They are typically smaller than 10 mm and frequently multiple, though they can be single.[17] They are known to be closely related to prolonged use of proton pump inhibitors.[18] They are mostly benign and have malignant potential in polyposis syndromes.[19] The frequency of FGPs varies between 6.1% and 77% in the literature.[3,7] In our study, we found this rate to be 10.7%. In our study, all FGPs were smaller than 10 mm and 95.8% were smaller than 5 mm. There was no significant relationship between FGPs, and gender and also HP. Intestinal metaplasia was not detected in any cases with FGPs. More than one polyp was present in 70.8% of cases with FGPs.

Neuroendocrine tumors of the stomach are extremely rare and originate from enterochromaphine-like cells in the gastric fundus and corpus mucosa.[20] Gastric neuroendocrine tumors are relatively rare and they are three types; type I, II, and III. These are histologically slowly progressive tumors. Metastasis via muscular layer is infrequent and observed in relatively large lesions. Therefore, endoscopic ultrasonography is required to assess invasion, prior to polypectomy. Annually endoscopic examination is recommended for the follow-up.[21] They are common in females and at advanced age. In a retrospective study, the frequency of neuroendocrine tumor in patients with gastric polyps was found to be 3.5%, the mean age was 49.9 years, and the female/male ratio was 2.3/1.[5] In our study, one of the neuroendocrine tumors was detected in the cardia and five were detected in the corpus; neuroendocrine tumors constituted 2.4% of the cases with gastric polyps. In addition, we found the mean age of occurrence to be 63 years, and the female/male ratio was found to be 5/1. More than one polyp was present in 83.3% of cases with neuroendocrine tumor and it was statistically significant. Our data supports the literature.

The facts that our patients could not be followed up as the study was a retrospective study, HP could not be tested in all patients who were found to have polyps, and the study was a single-center study, were all limiting factors.

Conclusion

We found that the most frequently detected polyps in the stomach were HPs, the majority of

the cases had single polyps, most of the polyps (%90) were smaller than 5 mm, and polyps were found most commonly in the corpus and least commonly in the antrum. Our study included the highest number of cases with gastric polyps conducted in Turkey's eastern and southeastern regions, and it completed studies conducted previously on this issue in Turkey.

Conflict of Interest

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Study Conception: NE, BE; Study Design: FB[3], BE; Supervision: EA, IS; Materails: NE; Data Collection and/or Processing: EA; Statistical Analysis and/or Data Interpretation: BE; Literature Review: FB[3], FB[6]; Manuscript Preparation: NE; Critical Review: FB[6].

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Original Article

Evaluation of Insulin Resistance and Vitamin D Levels in Patients With Polycystic Ovary Syndrome

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ABSTRACT

Background Polycystic ovary syndrome (PCOS) is associated with many long term health problems such as increased risk of obesity, type 2 diabetes, metabolic syndrome and cardiovascular risk factors. Several reports indicated that PCOS patients have lower vitamin D status compared to healthy subjects. In our study we aimed to investigate whether vitamin D deficiency has effect on the pathogenesis of insulin resistance in PCOS.

Material and Methods Fourty eight patients with PCOS and 24 healthy controls were included in the study. Following the physical examination and anthropometric measurements of the patients and healthy subjects, glycemic control data, lipid values, parathormone, vitamin D status and hormonal parameters were studied.

Results In our study, vitamin D levels were significantly lower in PCOS patients (19.7±26.9 ng/mL) compared with controls (31.9±35 ng/mL, $p<0.01$). Vitamin D levels were found to be lower in the obese PCOS group compared to those with non-obese, but not significant. Statistically significant inverse correlation was found between vitamin D levels and body mass index (BMI). It was also found between vitamin D and low density cholesterol (LDL-C).

Conclusions Our findings revealed increased likelihood of metabolic and dyslipidemic manifestations in PCOS patients compared to control group, while no significant difference was noted in vitamin D levels among PCOS patients in terms of co-morbid obesity. The detection of lower vitamin D levels in PCOS patients suggested that this may be one of the causes of insulin resistance and metabolic complications in these patients.

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases in women of reproductive age with an incidence of 5-15%.[1] The prevalence of PCOS may change depending on the criteria used for diagnosis and decrease with age.[2] The Rotterdam criteria frequently used for the diagnosis of PCOS include the presence of polycystic ovaries on ultrasound with oligomenorrhea or oligo-ovulation, clinical and/or biochemical hyperandrogenism. After excluding other causes of hirsutism, the presence of the two criterias, enough for diagnosis as PCOS.[3]

Although the etiology of PCOS is not well known despite intensive research, it is known that inflammation leading to oxidative stress and endothelial damage with genetic factors play a role in the ethiopathogenesis of the disease.[4] Chronic inflammation in PCOS is thought to cause a potential link between PCOS and long-term metabolic and cardiovascular complications.[5]

PCOS is associated with many long term metabolic and cardiovascular problems such as increased risk of obesity, type 2 diabetes and cardiovascular risk factors.[3] Moreover, it was reported that dyslipidemia and metabolic syndrome is higher in PCOS patient with insulin resistance (IR) compared to those without IR.[6] Hyperinsulinemia causes excess production of several adipokines such as leptin, adiponectin and resistin. These adipokines play a role in intraabdominal fat accumulation and diabetogenic processes.[7]

Vitamin D is a lipid solubl molecule that accumulates in adipose tissue. It also has it's receptors in human ovaries, endometrium, placenta and decidual cells. Previous reports indicated that PCOS patients have lower vitamin D status compared to healthy subjects.[8,9] Moreover, It has been suggested that vitamin D deficiency may be associated with metabolic disorders in PCOS.[10,11] The association between vitamin D levels and IR since a causative relation from a pathological point of view cannot be given due to the study design. In our study we aimed to investigate whether vitamin D deficiency has effect on the pathogenesis of IR in PCOS.

Material and Methods

A total of 72 subjects, 48 of whom were PCOS patients and 24 healthy participants, were included in the study. The PCOS group consisted of patients who were diagnosed with PCOS according to the 2004 revised Rotterdam Criteria. Provided that releated disorders are excluded, the patients who had two out of the following could be diagnosed as PCOS; ovulatuar disturbance, hyperandrogenism (clinical and/or biochemical) and polycystic ovaries confirmed via ultrasonography (USG). Hirsutism was evaluated using Ferriman–Gallwey score and menstrual disturbance (none, oligomenorrhea, amenorrhea) was evaluated based on medical history in all subjects. We excluded pregnant women, women with incomplete PCOS diagnosis and received hormone preparations such as oral contraseptive drugs within the last six months. Twenty-four healty subjects participated in the study. The study was performed in accordance with the Helsinki Declaration, and approved by the local ethical committee of our institution. Written informed consent was obtained from all the participants.

Data on antropometric measurements were recorded in each participant. Body mass index (BMI) was calculated based on weight and height (weight/height^2). For subgroup comparisons, patients with a BMI of 30 and above were classified as obese-PCOS, and those below 30 were classified as non-obese PCOS. Weight measurement was done with a classic weighing machine. Waist and hip circumference was performed with an inelastic tape measure while the patients were standing upright. Body fat ratio was measured with a body analyzer using the bioelectrical impedance method. Patient files were analyzed in detail and plasma levels of glycemic and lipid parameters, vitamin D, parathormone and other hormonal parameters were recorded. IR status was evaluated by calculating the homeostatic model assessment for IR (HOMA-IR).

Statistical Analysis

SPSS version 21 (IBM corp) program was used for statistical analysis. Demographic, basal characteristics and vitamin D levels are summarized with mean±standard deviation for

continuous variables, frequency and percentages for categorical variables. Chi-square test was performed for comparison of the categorical data. The continuous data between the study and control groups were analized with Student's t test for normally disturbed variables and Mann–Whitney U variance analysis tests for not normally distributed others. Two-way Spearman's correlation analysis was used to examine the relationship between variables. The significance level of p value less than 0.05 was regarded as statistically significant.

Results

Mean age were insignificant between the two groups. The mean body weight, BMI and body fat ratio of the PCOS patients were 76.2±20.2 kg, 28.7±7.8 kg/m^2 and 35.6±9.4% respectively. In the control group, mean body weight, BMI and body fat ratio of the patients were 61.5±7.5 kg, 22.1±2.6 kg/m^2 and 28.1±5.4%, respectively. Body weight, BMI and body fat ratio were found to be significantly higher in the PCOS group. Waist and hip circumference were measured as 85.9±16.9 cm and 105.0±13.0 cm in the PCOS group, 74.2±5.9 cm and 96.2±6.2 cm in the control group, respectively. Waist and hip circumference values were found to be significantly higher in the PCOS group. While systolic blood pressure (SBP) was similar in both groups, diastolic blood pressure (DBP) measurements were statistically significantly higher in the PCOS group *(Table 1)*.

Plasma fasting glucose levels were significantly higher in PCOS group. HOMA-IR values which is an indication of IR were also higher in the PCOS group, as expected (p <0.001). Low density cholesterol (LDL-C) and triglyceride levels were higher and High density cholesterol (HDL-C) levels were lower in the PCOS group compared to the controls. Vitamin D levels were 19.7±26.9 ng/mL and 31.9±35 ng/mL in the PCOS and control groups, respectively. The difference between the two groups was statistically significant. In the hormonal evaluation; the level of total testosteron, dehydroepiandrosterone-sulphat (DHEA-S) and androstenedione were statistically significant higher in PCOS patients. *(Table 2)*.

When PCOS patients were subclassified as obese and nonobese, SBP and DBP found to be higher in the obese PCOS group. Obese PCOS group had higher levels of fasting blood glucose (FBG), LDL-C and triglycerides and lower levels of HDL-C levels compared to nonobes PCOS. The mean HOMA-IR was 3.6±1.5 in the obese PCOS group, while it was 1.8±0.8 in the non-obese PCOS group. Results were statistically significant. Vitamin D levels were found to be lower in the obese group but not significant (13.7±8.0 vs. 25.7±36.6 ng/mL) *(Table 3)*. In the

Table 1. Comparison of demographic data of the patients according to the groups.

	PCOS group (n=48)	Control group (n=24)	p value
Age (year)	26.8±7.1	28.2±4.2	0.1
Height (cm)	162.3±5.8	165.2±7.7	0.09
Weight (kg)	76.2±20.2	61.5±7.5	0.008*
BMI (kg/m^2)	28.7±7.8	22.1±2.6	0.003*
Waist circumference (cm)	85.9±16.9	74.2±5.9	0.03*
Hip circumference (cm)	105.0±13.0	96.2±6.2	0.009*
Waist-hip ratio	0.81±0.08	0.76±0.03	0.07
BFR (%)	35.6±9.4	28.1±5.4	0.001*
SBP (mmHg)	116.6±13.6	110.8±11.0	0.06
DBP (mmHg)	76.0±8.9	69.5±9.0	0.006*

*p <0.05, BMI: body mass index, BFP: body fat ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure.

correlation analysis, a statistically significant inverse correlation was found between serum vitamin D levels and BMI values in the PCOS group (r=[-0.243], p=0.04), however, no correlation was found between vitamin D levels and HOMA-IR scores. In addition, while there was an inverse correlation between vitamin D and LDL-C (r=[-0.242], p=0.04), no significant correlation was found between vitamin D levels and other lipid parameters.

Discussion

PCOS, which is common in women of reproductive age, causes metabolic disturbances as well as reproductive disorders. Obesity, IR, dyslipidemia, and hypertension are seen in patients with PCOS and these pose a risk in terms of diabetes and cardiovascular diseases.[12] Approximately 30% of PCOS women are obese.[13] In our study, mean BMI was 28.7±7.8 kg/m² in PCOS group and it was statistically significantly higher than healthy control group. Waist and hip circumference and body fat ratio were significantly higher in PCOS patients. In our study, SBP was similar in both groups, while diastolic blood pressure measurements were significantly higher in patients with PCOS. In our study, LDL-C and triglyceride levels were higher and HDL-C levels were lower in the PCOS group. In addition, higher triglyceride and LDL-C levels and lower HDL-C levels were detected in the obese PCOS group compared to the non-obese PCOS group.

Accumulating evidence has shown that the prevalence of vitamin D deficiency is higher in women with PCOS compared to healthy controls.[9] Vitamin D deficiency is reported to be between 20-48% in the general population, and 67-85% in patients with PCOS.[14] Voulgaris *et al*.[15] shown that vitamin D levels were lower in obese women with

Table 2. Comparison of laboratory data of the patients according to the groups.

	PCOS group (n=48)	Control group (n=24)	p value
FBG (mg/dL)	86.8±9.2	73.4±12.2	0.000*
PPG (mg/dL)	96.0±19.7	75.1±13.6	0.000*
HDL-C (mg/dL)	50.5±12.1	58.7±9.9	0.001*
LDL-C (mg/dL)	117.5±37.2	97.0±18.9	0.06
TG (mg/dL)	115.4±83.4	68.1±21.0	0.006*
TG/HDL-C	2.5±2.4	1.1±0.4	0.002*
ALT (U/L)	16.8±8.5	16.0±8.8	0.6
Insulin (IU/mL)	12.7±6.6	6.7±2.4	0.000*
HOMA-IR	2.7±1.5	1.2±0.4	0.000*
Vitamin D (ng/mL)	19.7±26.9	31.9±35	0.005*
PTH (pg/mL)	79.6±29.9	55.6±22.6	0.000*
FSH (mIU/mL)	5.4±5.1	5.7±4.9	0.6
LH (mIU/mL)	8.9±12.6	5.7±7.2	0.04*
E2 (pg/mL)	104.2±102.9	64.0±44.6	0.09
Testosteron (ng/mL)	0.6±0.4	0.4±0.3	0.000*
DHEAS (µg/dL)	369.2±141.0	268.5±116.1	0.005*
Androstenedione (ng/mL)	4.0±1.4	2.2±0.9	0.000*

*p <0.05, FBG: fasting blood glucose, PPP: postprandial glucose, HDL-C: high density cholesterol, LDL-C: low density cholesterol, TG: triglyceride, ALT: alanine transaminase, HOMA-IR: homeostasis model assessment, PTH: parathormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, E2: oestradiol, DHEAS: dihydroepiandrosterone sulfate.

PCOS than in non-obese women with PCOS. In our study, vitamin D levels were 19.7±26.9 ng/mL and 31.9±35 ng/mL in PCOS and control groups, respectively (p=0.005). When PCOS patients were classified as obese and non-obese, vitamin D levels were lower in the obesity group, but not significant (13.7±8.0 vs. 25.7±36.6 ng/mL).

The vitamin D receptor gene, which regulate approximately 3% of the human genome and vitamin D receptors, modulate the expression of many genes in various tissues, including the pancreas and ovaries. Thus, vitamin D has a wide range of effects including the effects on the metabolism of glucose and lipid, and the regulation of blood pressure.[16,17] Several reports suggest that some proinflammatory mediators, such as tumor necrosis factor, are important in pathogenesis of PCOS independent of excess weight. Hence, PCOS is currently considered as a chronic, low-grade inflammatory disorder.[18,19] Hyperglycemia and higher levels of free fatty acids can increase reactive oxygen species and oxidative stress, leading to dysfunction and cell death.[20]

The prevalence of IR approximately 50-70% in PCOS women.[16] Although serum insulin levels are lower in non-obese women with PCOS compared to obese ones, IR is a common clinical finding in these women.[21] In our study, plasma fasting glucose levels and HOMA-IR were significantly higher in PCOS with obesity compared to the control group. Similar statistically significant results was also present in PCOS with obesity compared to non-obese ones.

Increasing number of studies have shown that vitamin D and HOMA-IR levels are inversely related in PCOS.[16] Although the effects of vitamin D on glucose metabolism are not clear, it can be explained that it increases insulin synthesis and insulin receptor expression and decreases some inflammatory cytokines.[22] Hann *et al.*[23] reported that vitamin D levels were lower in women with PCOS who had IR. Wehr *et al.*[11] shown that vitamin D has been an independent predictor of IR and sensitivity. In our study, no significant relationship was found between IR and vitamin D levels in PCOS patients.

Table 3. Comparison of demographic and laboratory data of the PCOS patients according to the BMI.

	Obese PCOS group (n=24)	Non-obese PCOS group (n=24)	p value
SBP (mmHg)	124.7±12.5	108.5±9.2	0.000*
DBP (mmHg)	79.3±7.4	72.7±9.2	0.01*
FBG (mg/dL)	88.9±10.1	84.7±7.9	0.07*
PPG (mg/dL)	101.3±23.1	90.2±13.5	0.1
HDL-C (mg/dL)	43.9±8.9	57.3±11.2	0.000*
LDL-C (mg/dL)	128.7±37.5	105.8±33.8	0.01*
TG (mg/dL)	161.0±94.3	67.9±25.1	0.000*
TG/HDL-C	3.8±2.8	1.2±0.5	0.000*
ALT (U/L)	21.5±7.8	12.1±6.3	0.000*
Insulin (IU/mL)	16.5±7.0	8.7±2.7	0.000*
HOMA-IR	3.6±1.5	1.8±0.8	0.000*
Vitamin D (ng/mL)	13.7±8.0	25.7±36.6	0.2
PTH (pg/mL)	81.0±29.2	78.3±31.1	0.5

*p <0.05, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, PPP: postprandial glucose, HDL-C: High density cholesterol, LDL-C: Low density cholesterol, TG: triglyceride, ALT: alanine transaminase, HOMA-IR: Homeostasis model assessment, PTH: parathormone.

Based on accumulating reports, the relationship between vitamin D and obesity has been clearly demonstrated. Despite this, the causal relationship between low vitamin D levels and obesity remains unclear.[24] In a meta-analysis investigating the relationship between vitamin D deficiency and BMI, the prevalence of vitamin D deficiency in obese participants was found to be 35% higher than the non-obese group.[25] In another meta-analysis, vitamin D deficiency prevalence was correlated with obesity in Asians (OR 95% CI 3.70 [1.98-6.90]) and European-Americans (OR 95% CI 3.09 [1.89-5.04]).[26] In our study, a statistically significant relationship was found between low vitamin D and BMI.

Clinical studies have shown that vitamin D deficiency is related with arterial hypertension, due to the possible inhibitory effect of vitamin D on renin gene expression.[27] Wehr *et al.*[11] found significantly negative correlation of vitamin D levels SBP and DBP in PCOS patients. Dyslipidemia, with a prevalence of approximately 70%, is a frequent metabolic disorder in PCOS patients. Legro *et al.*[28] found significant elevations in LDL-C levels in women affected by PCOS, independent of obesity. Similarly, several studies have found an association between low vitamin D levels and increased total cholesterol, LDL-C, triglycerides, and low HDL-C.[29-31] In our study, an inverse relationship was found between vitamin D and LDL-C, but no significant relationship was found between vitamin D and other lipid parameters.

Limitations

Our study has a few limitations that should be noted. One of the major limitations of our study was its evaluation of IR with HOMA-IR. Secondly, the sample size was small.

Conclusions

As a conclusion, in our study, we showed that vitamin D levels were lower in PCOS patients and suggested that this may be one of the causes of IR and metabolic complications in these patients. A statistically significant relationship was found between BMI and low vitamin D levels. It was also found inverse correlation between vitamin D and LDL-C. However, our study revealed that IR increased in women with PCOS, but there was no significant relationship between IR and vitamin D levels.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors' Contribution

Study Conception: OOG; Study Design: OOG; Supervision: OOG, SC; Data Collection and/or Processing: OOG, PS, SC; Statistical Analysis and/or Data Interpretation: SC, OOG; Literature Review: PS; Manuscript Preparation: PS; and Critical Review: OOG, SC.

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Original Article

Clinical, Radiological and Laboratory Features and Treatment Responses of COVID-19 Diseases in Pregnant Women

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ABSTRACT

Background SARS-CoV-2 is more contagious than other viruses among populations. Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia.

Material and Methods Thirty-two pregnant women who were diagnosed with COVID-19 disease by PCR test in our hospital between March 2020 and June 2020 were included in this study. Patients' complaints, comorbid disorders, general physical conditions, radiological, laboratory characteristics, treatment results and maternal and fetus health were recorded retrospectively.

Results The mean age of the patients was 26.6 years. Pregnancy-induced hypertension was evident in 2 patients (6.2%), preeclampsia in 1 patient (3.1%), asthma in 1 patient (3.1%). Mostly detected complaints were cough (34.4%) and fatigue (31.3%). The most frequent abnormal laboratory findings were high fibrinogen level (80.9%), high D-dimer level (71.4%), high CRP level (58.1%). Lymphopenia was found in 15.6% of patients. The maternal and fetal mortality rate was 0%. The rate of improvement in laboratory values in response to the treatment was as follows respectively; sodium (92.3%), lymphocyte count (80%), LDH (62.5%), CRP (61.1%), D-dimer (25%). None of the patients developed spontaneous abortion. Cesarean delivery was performed in 15.6% of patients. 5 newborns were negative for the COVID-19 PCR test two times.

Conclusions Mostly detected complaints in pregnancy patients with COVID-19 disease were cough and fatigue. While evaluating the treatment response, the improvement in sodium level may be more valuable than the improvement in acute phase reactants. The prognosis was quite good in mothers and children treated for this disease. The vertical transition of the disease could not be demonstrated.

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Introduction

Coronaviruses are enveloped, non-segmented, positive-sense ribonucleic acid (RNA) viruses belonging to the family Coronaviridae, order Nidovirales.[1] Pneumonia caused by COVID-19 is a highly contagious and infectious disease declared a health emergency by the World Health Organization.[2-4] Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia, because of the physiologic changes in the immune and cardiopulmonary systems (e.g. diaphragm elevation, increased oxygen consumption, and oedema of respiratory tract mucosa), which can render them intolerant to hypoxia.[5] Despite some COVID-19 guidelines, some clinical questions about pregnancy and childbirth remain unanswered.[6] The rate of COVID-19 in pregnant women and pregnant women who applied to the hospital for any reason or were newly admitted to the hospital was around 10%. In general, pregnancy does not significantly increase the risk of becoming infected with SARS-CoV-2.[7] The World Health Organization (WHO) has stated that pregnant women or women who are recently pregnant, older, overweight, and have pre-existing medical conditions such as hypertension and diabetes have an increased risk of developing severe COVID-19.[8] In general, there is a consensus that breastfeeding should be encouraged because of its mutual benefits. However, whether the virus can be transmitted through breast milk is not yet known.[9] In present study, we investigated clinical, radiological, laboratory characteristics, treatment results of pregnant women with the covid disease, and its effects on maternal and fetus health.

Material and Methods

Thirty-two patients who were diagnosed as COVID-19 disease by PCR test in our hospital between March 2020 and June 2020 were included in this study. Ethics approval and consent to participate: For this study, approval was obtained from the clinical research ethics committee of the Bursa higher specialized education and research hospital. Ethics committee approval code: 2011-KAEK-25 2020/05-05. Patients' ages, pregnancy weeks, complaints, comorbid diseases, general physical conditions, oxygen saturation level recorded with pulse oximeter, laboratory and radiological findings were recorded retrospectively.

The duration of hospitalization of patients was recorded. Clinical, laboratory responses to the treatment given patients during hospital stay, need for intensive care and mortality rate, if any, were determined. Need for cesarean section (C/S) as a complication of COVID-19 disease was also recorded. If the patients gave birth to children (spontaneous labor or with C/S), the condition of these children and whether covid disease was detected in this children were also recorded.

Results

Patients' ages ranged from 17 to 39. The mean age of them was 26.6±5.7 years (mean±SD). Four patients (12.5%) had comorbid diseases. Pregnancy-induced hypertension was evident in 2 patients (6.2%), preeclampsia in 1 patient (3.1%), asthma in 1 patient (3.1%). The gestational weeks of the patients ranged from 8 to 38 (mean 21.3±10.2). The seven patients (21.9%) had no complaints in the anamnesis and signs. The other 25 (78.1%) had complaints. No sputum was detected in any patient. The incidence of other complaints was shown in Table 1. The general clinical condition of 31 patients (96.9%) was good at presentation.

Table 1. Rates of complaints detected in COVID-19 patients.

Complaints	n (%)
Cough	11 (34.4)
Fatigue	10 (31.3)
Headache	5 (15.6)
Joint pain	5 (15.6)
Sore throat	4 (12.5)
Dyspnea	4 (12.5)
Fever	3 (9.4)
Anorexia	2 (6.3)
Diarrhea	2 (6.3)
Nausea	2 (6.3)
Anosmi	2 (6.3)
Taste inability	1 (3.1)
Taste inability+ anosmi	1 (3.1)
Chest pain	1 (3.1)
Vomiting	1 (3.1)
Palpitation	1 (3.1)

Table 2. Laboratory findings of pregnant patients with COVID-19 on admission.

Parameters	Mean (min:max)	Patient number higher than normal n (%)	Patient number lower than normal n (%)
WBC count (/mm^3)	6,989 (4,000:11,900)	4 (12.5)	-
Platelet count (/mm^3)	210,968 (46,000:391,000)	-	5 (15.6)
Hemoglobin (g/dL)	11.4 (5.9:13.9)	-	18 (56.3)
Leucocyte count	5,200 (2,400:8,600)	2 (6.3)	-
Leucocyte (%)	69 (40.9:85)	7 (21.9)	2 (6.3)
Lymphocyte count	1,568 (470:3,000)	-	5 (15.6)
Lymphocyte (%)	23.1 (7.7:48)	2 (6.3)	10 (31.3)
Eosinophil count	0.06 (0:0.57)	2 (6.3)	-
Eosinophil (%)	0.8 (0:4.7)	-	-
Basophil count	0.01 (0:0.08)	-	-
Basophil (%)	0.25 (0.1:0.9)	-	-
CRP (mg/L)	14 (3.1:143)	18 (58.1)	-
Ferritin (ng/mL)	137.3 (7.6:3133)	1 (3.4)	6 (18.8)
D-dimer (ng/mL)	1.38 (0.21:5.47)	20 (71.4)	-
LDH (U/L)	220.2 (122:734)	8 (27.6)	3 (9.4)
Troponin (ng/mL)	2.4 (2:7.8)	-	-
Fibrinojen (mg/dL)	455 (139:688)	17 (80.9)	-
Creatinine (mg/dL)	0.47 (0.28:0.69)	-	-
AST (U/L)	19.2 (11:35)	-	-
ALT (U/L)	14.8 (2:53)	-	-
Sodyum (mEq/L)	135.5 (126:141)	-	13 (41.9)
Potasyum (mEq/L)	3.9 (3.07:4.65)	-	2 (6.5)

Only one patient (3.1%) had a moderate clinical condition. In addition, only one patient (3.1%) had a low oxygen saturation level of 92%, and all the other patients had normal oxygen saturation levels.

Laboratory findings of pregnant patients with COVID-19 are shown in Table 2. Fibrinogen level was studied in 21 patients, and its level was high in 17 patients (80.9%). Laboratory abnormalities are in order according to the frequency of occurrence; high fibrinogen level (80.9%), high D-dimer level (71.4%), increased C-reactive protein (CRP) level (58.1%), low haemoglobin level (56.3%), low sodium level (41.9%), low lymphocyte (31.3%), high lactate dehydrogenase (LDH) level (27.6%), low lymphocyte count (15.6%), low platelet count (15.6%). It was interesting that only one patient had high ferritin levels. Ferritin levels were found below average in 6 patients (18.8%) *(Table 2)*.

The radiological examination was requested in 5 of the patients. Thoracic CT was performed in 4 patients, and a posterior-anterior chest X-ray was performed in 1 patient. On thorax CT, only one patient had bilateral multifocal, peripheral, basal dominant significant ground-glass opacities and consolidations *(Figure 1)*. The other 4 had no infiltration.

Treatment protocols for these pregnant patients with COVID-19 were listed in Table 3. Hydroxychloroquine (HCQ) treatment alone was the most common treatment protocol (78.1%). One patient had to be given tocilizumab treatment after HCQ treatment. Antiviral treatment was not given to 2 patients *(Table 3)*. One patient (3.1%) needed intensive care, and none died. Length of stay in the hospital (LOS) ranged from 3 to 20 days. The average LOS was 6.1 days.

Table 3. Treatment protocol.

Protocol	n (%)
Hyroxychloroquine	25 (78.1)
Hyroxychloroquine+azithromycin	2 (6.3)
Lopinavir+ritonavir	1 (3.1)
Azithromycin	1 (3.1)
Hyroxychloroquine+tocilizumab	1 (3.1)
Without drug treatment	2 (6.3)

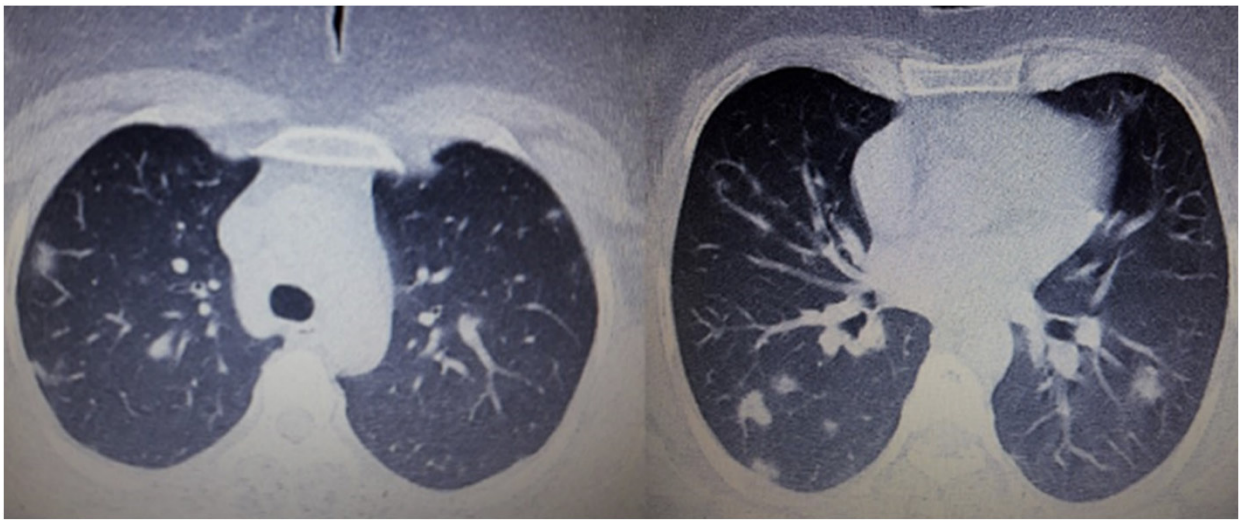

Figure 1. Thorax CT: bilateral, multifocal, peripheral, basal-predominant ground-glass opacities and consolidations.

Laboratory response rates to treatment for COVID-19 disease were shown in Table 4. The rate of improvement in laboratory values in response to the treatment was as follows respectively; sodium (92.3%), lymphocyte count (80%), LDH (62.5%), CRP (61.1%), D-dimer (25%). Ferritin level was elevated in only one patient and returned to normal with treatment *(Table 4)*. None of the patients developed spontaneous abortion. Cesarean section was delivered in 5 patients (15.6%). 2 had pregnancy-induced hypertension, 1 had preeclampsia, 1 had placenta previa, and 1 had a non-reactive contraction in NST. 2 patients (6.3%) had preterm cesarian delivery at 35 weeks gestation. Five newborns were negative for the COVID-19 PCR test two times.

Table 4. Laboratory response rates to treatment for COVID-19 disease.

Parameters	n (%)
Leukocyte	3 (75)
Lymphocyte	4 (80)
Platelet	3 (60)
CRP	11 (61.1)
Ferritin	1 (100)
D-dimer	5 (25)
LDH	5 (62.5)
Fibrinogen	4 (23.5)
Sodium	12 (92.3)
Potassium	1 (50)

Discussion

SARS-CoV-2 is more contagious than other viruses among populations. Pregnant women could be more susceptible to COVID-19 infection than the general population. Our study mostly detected cough complaints (34.4%) and fatigue (31.3%). Pain in different parts of the body (headache, joint pain and chest pain) was also detected in a substantial proportion of the patients (34.4%). Anosmia or/ and taste inability complaints were seen at a rate not negligible (12.5%). However, contrary to expectations, fever symptoms were detected at a very low rate (9.4%). In the study of Yan J *et al.*[5], fever was the most common sign detected in 50.9% of patients, cough in 28.4%, fatigue in 12.9%. In another study, fever was detected in 84% of patients and cough in 28%.[10] Shortness of breath was seen in 18% of pregnant patients in a study[10], but it was in 12.5% in this study. The rate of asymptomatic patients in our study was 21.9%, similar to the rate (23.3%) found in their research.[5]

In this study, the most frequent abnormal laboratory findings were high fibrinogen level (80.9%), high D-dimer level (71.4%), high CRP level (58.1%). While lymphopenia was found in two-thirds of patients in previous studies,[3,5,11-13] this rate was relatively low in our study at 15.6%. Interestingly, the rate of a low percentage of lymphocytes (31.3%) was higher than the low rate of lymphocytes count (15.6%). There was thrombocytopenia in 5 patients (15.6%); it was 13% in a recent study.[10] Interestingly, ferritin level was

high in only one patient, and ferritin levels were found below the expected values in 6 (20.7%) of 20 patients who evaluated ferritin levels. Leucocytosis was detected in 21.9% of patients, and this rate was higher in another study, such as 80%.[10]

Since the patients were pregnant, only five patients could be evaluated radiologically for fear of radiation side effects. Only 1 of these patients had pneumonia with diffuse infiltrations in both lungs *(Figure 1)*. In the study of Yan J *et al.*[5], there were abnormal radiologic findings in 96.3% of cases.

Recent studies have identified remdesivir and chloroquine as potential candidate drugs for the treatment of COVID-19.[14] Chloroquine phosphate is a ubiquitous antimalarial quinolone compound with broad-spectrum antiviral and immunomodulating activity. It has been shown to block coronavirus infection by increasing the endosomal pH required for cell fusion and interrupting the glycosylation of cellular receptors of SARS-CoV in cell culture.[14] In this study, hydroxychloroquine treatment alone was the most preferred form of treatment (78%). And this form of treatment was sufficient in the treatment of the majority of patients. However, despite HCQ treatment in 1 patient, when clinical laboratory improvement could not be achieved, tocilizumab treatment had to be given. With HCQ treatment, only one patient developed liver enzyme elevation as a side effect and improved when we stopped taking the drug.

The laboratory values that improved at the highest rate with treatment respectively were; sodium (92.3%), lymphocyte count (80%), leucocyte count (75%), LDH (62.5%), and CRP (61.1%). The recovery rate in D-dimer levels only remained at 25%. Also, the fibrinogen response rate remained at low levels of 23.5%. These results suggest that improvements in sodium, lymphocyte, leucocyte, LDH, and CRP values are quite sensitive while determining the response to treatment. In contrast, improvements in D-dimer and fibrinogen levels are not satisfactory. It has already been reported in previous studies that D-dimer levels are difficult to interpret, as the values are usually raised in pregnancy, such that only 84%, 33%, and 1% of women in the first, second, and third trimesters, respectively would have normal results based on conventional thresholds.[15] While evaluating the treatment response, the results of this study suggest that the improvement in sodium level may be more valuable than the improvement in acute phase reactants.

In the present study, the general clinical condition of almost all patients (96.9%) was good at presentation except for one. All mothers and infants showed good outcomes. One of the patients (3.1%) was taken to the intensive care unit and had to be given tocilizumab. None of the patients died. Similar results were found in the literature.[5,6] A case series of 12 pregnant women with SARS-CoV reported three maternal deaths in China.[16]

A total of 5 patients had C/S, which was thought to be a complication of COVID-19 disease. The reason for cesarean delivery in 2 of these patients was pregnancy-induced hypertension, preeclampsia in 1, placenta previa in 1 and nonreactive nonstress test in the other one. It has been reported that viral pneumonia in pregnant women is associated with an increased risk of preterm birth, fetal growth restriction (FGR), and perinatal mortality.[17] Based on the nationwide population-based data, it has been indicated that pregnant women with viral pneumonia other than COVID-19 (n=1,462) have an increased risk of preterm birth, FGR, and having a newborn with low birth weight and Apgar scores <7 at 5 minutes compared with those without pneumonia (n=7,310).[18] Our study suggests that the risk of spontaneous abortion is not increased in pregnant women with COVID-19 infection. This result is similar to the result of the study of Yan J *et al.*[5] The present study's findings also suggest that COVID-19 disease may increase the risk of preterm delivery before 37 weeks gestation. The rate of spontaneous abortion was 12.5% in the study of Yan J *et al.*[5] The fact that the PCR test for COVID-19 was negative in all five born children in our study created an impression that there was no vertical transition of this disease as in the study of Yan J *et al.*[5] Two recent research letters reported that three children had negative viral nucleic acid results. Still, the possibility of vertical transmission was thought as the immunoglobulin G, and immunoglobulin M tests were positive.[19,20] However, Yan J *et al.*[5] evaluated amniotic fluid, cord blood, and neonatal pharyngeal swab samples at birth to ascertain the possibility of vertical transmission, and their results indicated that SARS-CoV-2 was negative in all of the above

biological samples, suggesting that no intrauterine fetal infection occurred because of SARS-CoV-2 infection. In the study by Yu *et al.*[21], three neonates were tested for SARS-CoV-2, of whom two were negative. One neonate was positive, but the viral nucleic acid tests of the placenta and cord blood, in this case, were negative.[21]

Conclusion

The findings we obtained in our study were as follows: Mostly detected complaints in pregnancy patients with COVID-19 disease were cough and fatigue. HCQ treatment alone in covid treatment was successful; Improvement in sodium, lymphocyte, LDH, and CRP values in determining response to treatment is probably valuable. While evaluating the treatment response, the improvement in sodium level may be more valuable than the improvement in acute phase reactants. Prognosis was quite good in mothers and children treated for this disease. COVID-19 disease may increase the risk of preterm delivery before 37 weeks. Vertical transition of the disease could not be demonstrated.

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Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: AS, ET, NK; Study Design: AEC, AS, NK; Supervision: YU, SYG, OD; Fundings and Materails: SD, AK, US, AS, ET, NK; Data Collection and/or Processing: SYG, OD, AK; Statistical Analysis and/or Data Interpretation: US, YU, SD; Literature Review: AEC, US, AK, SD; Manuscript Preparation: SYG, OD, ET; Critical Review: AK, AEC, AS.

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TURKISH JOURNAL OF INTERNAL MEDICINE

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Case Report

Marginal Zone Lymphoma Presenting in a Patient With Autoimmune Hemolytic Anemia: A Case Report

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ABSTRACT

While autoimmune hemolytic anemia (AIHA) is expected in non-Hodgkin's lymphomas, it is less common in marginal zone lymphoma. Sixty-year-old male patient was followed up with hemolytic anemia in our clinic and while the etiology was investigated, scattered nodes in the mediastinum and abdomen compatible with lymphoproliferative disease were observed on CT, and positive detection of CD5, CD19, CD20, CD22, CD45, HLA-DR, FMC-7 on flow cytometry sent from peripheral blood and a diagnosis of low grade B cell lymphoma (MZL) was made with the result of bone marrow pathology. We found it appropriate to present our MZL case because of its response to steroid treatment and its rare presentation with AIHA.

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Introduction

Autoimmune hemolytic anaemia (AIHA) is an anaemia group characterized by the production of antibodies against autologous erythrocytes.[1] It is divided into primary and secondary.[1] Secondary AIHA can usually be seen in lymphoproliferative diseases, measles, EBV and CMV infection, leukaemia, thymoma, and colon cancer.[2] The lymphoproliferative illness is the most common B-cell chronic lymphocytic leukaemia relationship, but the prevalence in other non-Hodgkin's lymphoma is lower.[3] One of these lymphomas is marginal zone lymphoma (MZL).[4] Herein, we presented a case of the MZL with AIHA

Case Report

A sixty-year-old male patient applied to our clinic with the complaint of fatigue for a month. He had a history of using dual antituberculosis drugs due to pulmonary tuberculosis 18 years ago and mild hepatosplenomegaly on physical examination. Peripheral lymphadenopathy could not be detected. In the laboratory tests at the time of diagnosis, hemoglobin 5.8 g/dL, MCV 104 fl, leukocyte 9.65x10^9/L, neutrophil 5.85x10^9/L, lymphocyte 3.19x10^9/L, platelet 3x10^9/L, corrected reticulocyte 8.39%, sedimentation rate 93 mm/hour, LDH 455 U/L, total/direct bilirubin 1.91/0.7 mg/dL, direct coombs (IgG and Cd3) 3+. anti-nuclear antibody (ANA) detected negative. We observed spherocytes in the erythrocyte series in the patient's peripheral smear *(Figure 1)*.

With AIHA diagnosis, the patient received 1 mg/kg/day methylprednisolone treatment. There was no finding of active disease in the consultation of chest diseases due to a history of tuberculosis. Thorax computed tomography (CT) showed a few lymph nodes below 1 cm in the mediastinum, and small intestine mesentery around the celiac trunk, and extensive lymph nodes in the left paraaortic area consistent with a lymphoproliferative disease on abdominal CT. In the first-month follow-up examinations of the patient, his anaemia improved, but lymphocyte increase developed. The flow cytometry sent from peripheral blood showed that CD5, CD19, CD20, CD22, CD45, HLA-DR, and FMC-7 were positive *(Figure 2)*. With the pre-diagnosis of non-Hodgkin's lymphoma, PET-CT was performed to screen for high involvement lymphadenomegaly. PET/CT in the excision according to lymphadenopathy was not detected. A diagnostic bone marrow biopsy was performed on the patient. The bone marrow pathology result was reported as low-grade B-cell lymphoma (MZL) partially suppressed under steroid therapy. The patient with hemoglobin 12.6 g/dL with treatment was considered steroid responsive. It was planned to stop by decreasing the steroid dose.

Discussion

MZL has first described in 1992.[5] The frequency of MZL appears to be around 1-2% of non-Hodgkin's lymphomas.[5] The median age at diagnosis is approximately 65 years, ranging from 30 to 90, without gender predominance.[6]

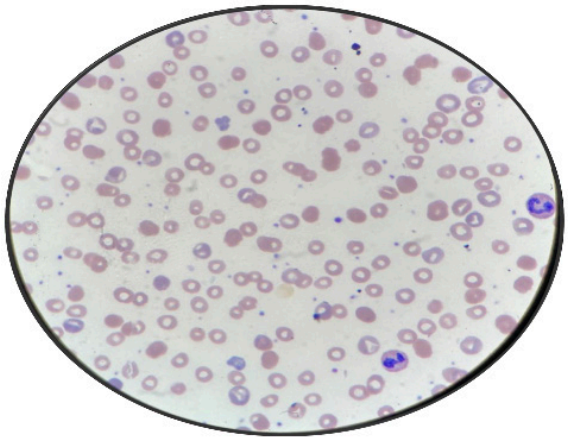
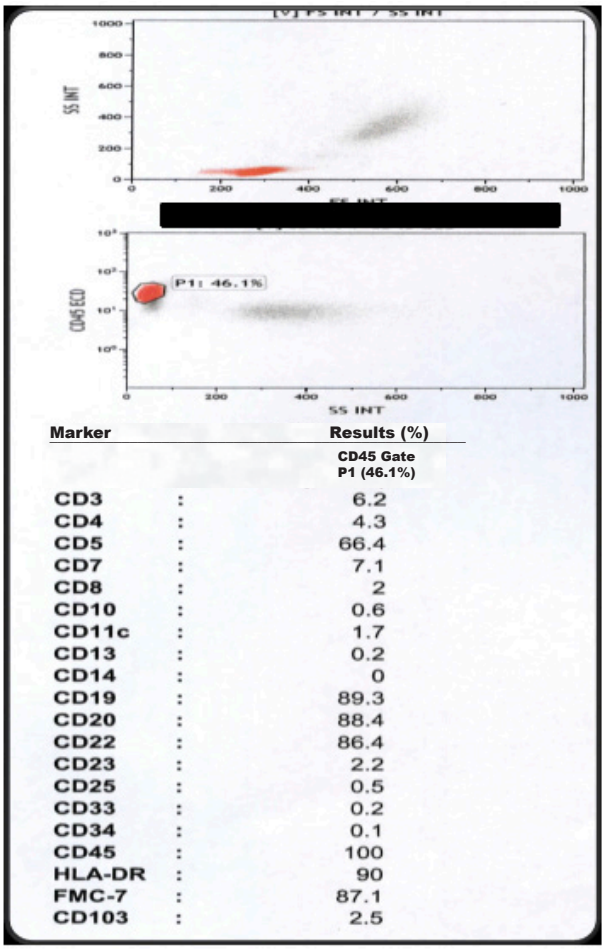


Figure 1. Spherocyte cells in the erythrocyte series in peripheral smear.



Marker	Results (%)
	CD45 Gate P1 (46.1%)
CD3	6.2
CD4	4.3
CD5	66.4
CD7	7.1
CD8	2
CD10	0.6
CD11c	1.7
CD13	0.2
CD14	0
CD19	89.3
CD20	88.4
CD22	86.4
CD23	2.2
CD25	0.5
CD33	0.2
CD34	0.1
CD45	100
HLA-DR	90
FMC-7	87.1
CD103	2.5

Figure 2. Flow cytometry sent from peripheral blood.

Almost without exception, MZL cases have bone marrow involvement at diagnosis, and roughly one-third have liver involvement.[6] In our case, mild hepatosplenomegaly was present, but no bone involvement was observed. The frequency of AIHA accompanying MZL has been reported as 10% and may be associated with chronic antigen stimulation and autoantibody formation.[2] In the study conducted by Zhou *et al.*[2] in 2020, 11 of 20 patients were followed up with AIHA before diagnosing lymphoma, while 8 were complicated with AIHA during non-Hodgkin lymphoma only one patient was diagnosed with AIHA and lymphoma simultaneously. It has been reported that 2 of these 20 patients belong to the MZL subgroup.[2] In the article published by Hauswirth *et al.*[7], 10 patients with MZL were discussed, and remission was observed after splenectomy in 7 patients and after rituximab treatment in 2 patients. At the same time, only 1 of them responded to steroid treatment.[7]

Conclusions

Our case is rare since MZL presents with AIHA and is responsive to steroids. Since it may be included in the presentation of AIHA lymphomas, patients who apply to the AIHA clinic should be examined for lymphoma.

Conflict of Interests

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Literature Review, Critical Review, Manuscript preparing held by all authors.

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Case Report

Acute Pulmonary Embolism in COVID-19 Disease: Case Report

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ABSTRACT

Inflammation, cytokine storm and lung damage associated with COVID-19 can cause the initiation of the thromboembolic process in patients. The 73-year-old male patient applied with sudden-onset shortness of breath to the emergency department of our hospital. Physical examination revealed an SpO_2 of 80% in room air, respiratory rate of 27/min. As the chest CT scan was compatible with COVID-19, the patient was admitted to the hospital and empirical treatment for COVID-19 was started, comprising of favipravir and dexamethasone. The RT-PCR of SARS-CoV-2 test resulted positive one day later. Due to the D-dimer value that was higher than expected in COVID-19, arterial blood gas compatible with thromboembolism, and the accompanying high lactate level, a CT angiogram was ordered and was compatible with pulmonary embolism, showing partial embolic filling defects in the lobar branches in the inferior lobes, and the lingular branch of the left lung. A closer investigation of pulmonary embolism in high-risk patients during the pandemics, and prescribing anticoagulant therapy starting on especially the first day of symptoms are vital to prevent potential complications of possible thromboembolism.

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Introduction

The recent novel coronavirus disease (COVID-19) is a complicated disease that can have a mild course or be accompanied by complications such as acute respiratory distress syndrome, shock, and multisystem organ failure that can result in death. It has been shown that venous thromboembolism may occur in the course of COVID-19. Disorders studied under that title include deep vein thrombosis, pulmonary embolism, ischemic cerebrovascular accident, and myocardial infarction.[1] The tendency for thrombosis have been related to prominent inflammation, hypoxia, immobilization, and disseminated intravascular coagulation.[2] The anticoagulant regime, which plays a key role in the treatment of COVID-19, can be vital should the differential diagnosis of dyspnea be skipped and pulmonary embolism missed.[3] We wanted to present a case that emphasizes the need to keep pulmonary embolism in mind when investigating the etiology of dyspnea in COVID-19.

Case Report

The 73-year-old male patient applied with sudden-onset shortness of breath to the accident and emergency department of our hospital. The patient stated that he had been treated for chronic obstructive pulmonary disease (COPD) for fifteen years and frequently suffered from shortness of breath especially in autumn and winter. The patient specified that he had no fever, malaise, or joint or muscle pain. Physical examination revealed an SpO_2 of 80% in room air, respiratory rate of 27/min, rhythmic pulse of 120/min, blood pressure of 160/80 mmHg, body temperature of 36.7 °C, and crackles in basal lobes and diffuse rhonchi in both lungs upon auscultation. Further laboratory investigations showed white blood cell (WBC) count of 16,180/mm^3, neutrophil ratio of 89.3%, lymphocyte ratio of 5.1%, C-reactive protein (CRP) of 15.73 mg/L, PT of 13.1 secs, INR 1.1, D-dimer >35.2 ug/mL, ferritin 315 ng/mL, albumin 2.50 g/dL, lactate dehydrogenase 340 IU/L, total bilirubin 1.42 mg/dL, direct bilirubin 0.67 mg/dL, troponin I 0.303 ng/mL, B-natriuretic peptide (NT-proBNP) 4,442 pg/mL, and Ca^{2+} of 8.10 mg/dL. Arterial blood gas values were pH of 7.352, pCO_2 32.8 mmHg, PaO_2 of 74.0 mmHg, HCO_3 act of 17.8 mmol/L, HCO_3 std of 19.1 mmol/L, Na^+ 134 mEq/L, K^+ 4.52 mEq/L, Ca^{2+} 1.16 mg/dL, glucose of 273 mg/dL, and lactate 7.13. A chest computed tomography (CT) scan was ordered so that the patient could be evaluated for COVID-19 and COPD. Moreover, a nasopharyngeal swab was performed for a COVID-19 real-time reverse transcription polymerase chain reaction (RT-PCR) of SARS-CoV-2 test. As the chest CT scan was compatible with COVID-19 *(Figure 1)*, the patient was admitted to the hospital and empirical treatment for COVID-19 was started, comprising of favipravir and dexamethasone. The RT-PCR of SARS-CoV-2 test resulted positive one day later.

Due to the D-dimer value that was higher than expected in COVID-19 (>35.2 ug/mL), arterial blood gas compatible with thromboembolism, and the accompanying high lactate level (7.13), a CT angiogram was ordered and was compatible with pulmonary embolism, showing partial embolic filling defects in the lobar branches in the inferior lobes, and the lingular branch of the left lung *(Figure 2)*. Echocardiography was normal. When the patient and his relatives were investigated further for the etiology of pulmonary embolism, the information received was that the patient suffered only from COPD, hypercholesterolemia, and inguinal hernia, that he had neither self nor family history of any coagulation disorders, that only his father had a history of cancer (prostate cancer), that coronary angiography had been performed twice on the patient but that he had not suffered from MI, that he had no history of trauma, and that he is mobilized during his daily life. Abdominal ultrasonography (USG) and bilateral lower extremity colour doppler USG were ordered to investigate the presence of any malignancy or deep vein thrombosis. Colour doppler USG showed a thrombus in the crural branches of the right popliteal vein. The repeated RT-PCR of SARS-CoV-2 test was negative on the 6^{th} day of hospitalization. The patient was discharged with 0.6 mg of enoxaparin bid once he had no need of oxygen support on his 17^{th} day of hospitalization.

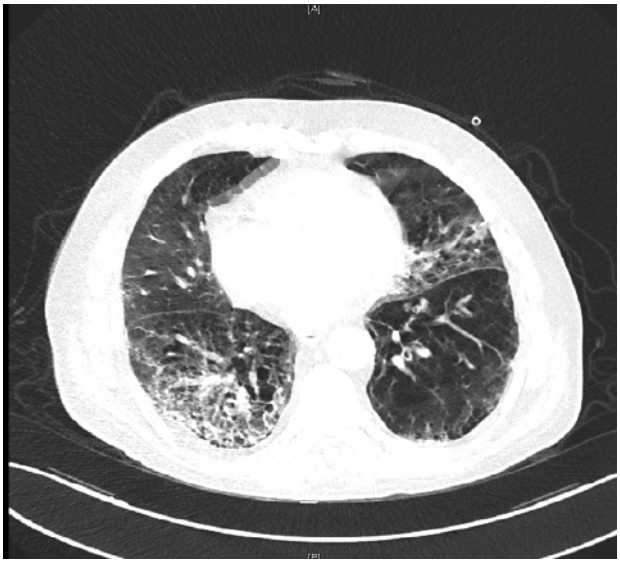

Figure 1. Chest CT scan with COVID-19.

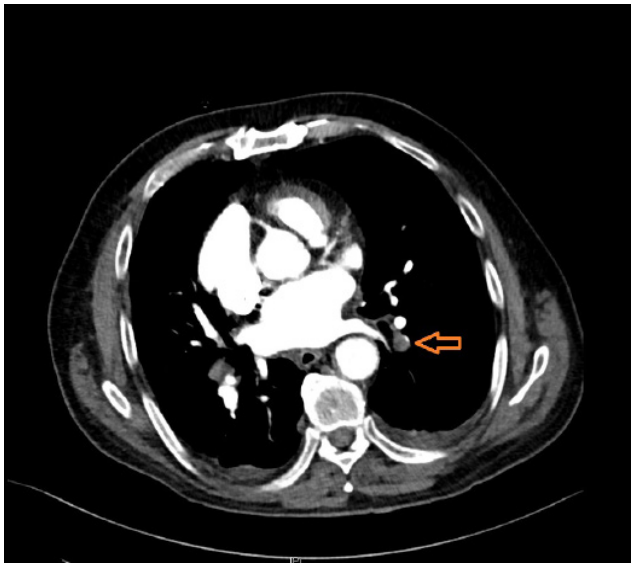

Figure 2. Partial embolic filling defects in the lobar branches in the inferior lobes (arrow).

Discussion

Recent studies have shown that pulmonary embolism was reported in 23-30% of COVID-19 patients who have undergone pulmonary CT angiography.[4] In our case, prominent increase in D-dimer levels led us to the diagnosis of pulmonary embolism. Similarly, the study conducted by Poyiadji *et al.*[5], showed that D-dimer levels were 9.33 µg/ml in average on patients with superimposed pulmonary embolism (n=72) as opposed to 1.33 µg/ml in those without.

In the retrospective study of Bompard *et al.*[6] 135 hospitalized COVID-19 patients were categorized as intensive care unit or ward patients. According to these parameters, the need for mechanical ventilation and D-dimer levels, the contrast-enhanced CT results of the patients were evaluated for pulmonary embolism. As a result, 32 of these 135 patients were diagnosed wih acute pulmonary embolism.[6] They concluded that contrast-enhanced CT should be preferred in suspicious COVID-19 patients presenting with high D-dimer levels. Thus, contrast-enhanced CT scan should be the first option in patients with dyspnea and high D-dimer levels.

A closer investigation of pulmonary embolism in high-risk patients during the pandemics, and prescribing anticoagulant therapy starting on especially the first day of symptoms are vital to prevent potential complications of possible thromboembolism. The delay of anticoagulant therapy in this patient, who resulted COVID-19 (-) on his 6th day of referral, was due to late application. Any patient older than 65 years should be investigated for D-dimer levels on their first day of symptoms and started an anticoagulant therapy accordingly.

Conflict of Interests

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Study Conception: YO; Study Design: YO; Supervision: YO; Data Collection: RG; Literature Review: BNC; Manuscript Preparation: NN.

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Case Series

Management of Immune Thrombocytopenic Patient Associated With COVID-19 Viral Infection: A Case Series

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ABSTRACT

Severe thrombocytopenia is a cause of morbidity and mortality for patients with COVID-19 infection. The common causes of thrombocytopenia in these patients are sepsis, drug-related, disseminated intravascular coagulation (DIC), heparin-associated thrombocytopenia (HIT), and microangiopathic hemolytic anemia (MAHA). Recently, cases of COVID-19 infection-associated immune thrombocytopenic purpura (ITP) have been reported in the literature. Herein, we presented our case series of 10 patients related to COVID-19.

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Introduction

The coronavirus disease emerged in December 2019 in Wuhan city of China. SARS-CoV-2 is a new type of RNA virus, affected more than 21 million people worldwide. The newly discovered coronavirus is a β-coronavirus with crown-enveloped virus particles.[1] The most common symptoms seen in COVID-19 infection are dry cough, fever, fatigue, joint pain and shortness of breath. Uncommon symptoms include diarrhea, headache, palpitations and chest pain. Hematological changes such as lymphopenia and thrombocytopenia are frequently observed in patients with COVID-19.[2] In a study involving 1099 patients, it was shown that 82.1% of the patients had lymphopenia, 36.2% had thrombocytopenia and 33.7% had leukopenia.[3] The platelet count is between 150-450,000 10^3/uL, below 100,000 10^3/uL is called thrombocytopenia. A comprehensive approach is required to diagnose COVID-19 infection-associated associated with COVID-19 infection after excluding several concomitant factors that may cause thrombocytopenia.[3] There are several hypotheses for the mechanism of thrombocytopenia in COVID-19. The first is that the virus infects bone marrow cells, leading to abnormal hematopoiesis. SARS-CoV-2 and HCoV-229E enter bone marrow

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cells and platelets via CD13 receptors and induce bone marrow growth inhibition and apoptosis, leading to abnormal hematopoiesis and thrombocytopenia.[4] The second is secondary hemophagocytic lymphohistiocytosis (HLH) and results from excessive proliferation and activation of the mononuclear macrophage system, in which inflammatory cytokines are released and large numbers of blood cells are engulfed. HLH has a rapid response with high mortality and causes cytopenia.[5] Another mechanism is the COVID-19 virus causes increased levels of autoantibodies and immune complexes, which can cause specific destruction of platelets by immune cells. One study reported that immune-mediated thrombocytopenia phenomenon is common in HIV-1 infected patients.[6] After excluding all causes of thrombocytopenia, ITP should be considered in the patient. Primary ITP is an acquired autoimmune disorder characterized by isolated thrombocytopenia caused by increased platelet destruction and impaired platelet production.[7] There is no definitive diagnostic test for ITP; therefore, primary ITP remains a diagnosis of exclusion after ruling out any underlying and/or initiating causes of the thrombocytopenia.[8] ITP is classified based on duration into newly diagnosed, persistent (3-<12 months), and chronic (≥12 months). Since the beginning of the pandemic, we have started to see case articles in the literature. According to the 2019 guideline of the American hematology community, a platelet count of less than 30,000 10^3/uL supports the diagnosis of ITP.[9] They recommend corticosteroids as first-line therapy for adult-onset ITP. 2020 recommendations of the UK hematology community: The standard first-line therapy for the treatment of acute ITP diagnosed for the first time or relapsed is prednisolone given at a dose of 1 mg/kg (maximum 80 mg) for 2 weeks and then stopped.[7] There is little data to show whether corticosteroids pose a higher risk of worsening symptoms after being infected with the COVID-19 virus. However, the first treatment option under WHO's guidance is alternative treatments rather than corticosteroids. The use of thrombopoietin receptor agonists (TPO-RAs) may be the preferred option first. Since the onset of the effect of TPO-RAs may take 7-14 days and in cases where urgent platelet elevation is required, intravenous immunoglobulin, CD20 inhibitor Rituximab, and thrombocyte suspensions in the presence of hemorrhage are recommended. Although patients with chronic ITP are not included in the high-risk group for COVID-19 infection, it recommends that patients with splenectomy be up-to-date with encapsulated bacteria vaccines.[9]

Material and Methods

Among the patients with thrombocytopenia (<30,000 10^3/uL) who were positive for the COVID-19 PCR test (polymerase chain reaction) from the declaration of the COVID-19 Pandemic (March 2020) to the present (August 2021), those with ITP diagnosis were included in the study. Viral markers (EBV, CMV, hepatitis, HIV etc.), tumor markers (CEA, CA-19.9, AFP, PSA etc.), autoimmune antibodies (ANA, anti-dsDNA, antiphospholipid, c3, c4 etc.) involved in the etiology of thrombocytopenia were sent from all patients. Peripheral blood smears were evaluated by internal medicine specialists and reported. Patients with positive tests other than PCR positivity were excluded from the study. Trauma history, pregnancy status, cancer patients, patients under 18 years of age, patients receiving anticoagulant, antiaggregant therapy, and chronic ITP patients were excluded from the study. Patients who developed thrombocytopenia after hospitalization were not included in the study, and these patients were excluded from the study because it was thought that drug-related thrombocytopenia could develop in the foreground. Patients whose chest tomography was compatible with COVID-19 viral pneumonia and whose PCR test was negative were excluded from the study. A total of 10 patients who met the criteria were reached. Our study involving human participation is in line with the 1964 Declaration of Helsinki and its subsequent amendments. The study is a case series and retrospective. According to the 2017 TUBA-clinical research phase studies and ethics committees workshop report, ethics committee approval is not required for case series included in retrospective studies. Patients who responded to the treatment were followed up in the internal medicine outpatient clinic for 12 months.

Table 1. The characteristics of the patients.

Patient	Age	Gender	Symptoms	Time/day elapsed	Initial platelet count (10^3/uL)	Comorbid disease	Treatment	Last platelet count (10^3/uL)	Prognosis	Treatment response day
1	79	Female	Asymptomatic	9	1,000	Diabetes, hypertension	Methyl-prednisolone	54,000	Exitus	-
2	84	Male	Melena	14	17,000	Dementia	Methyl-prednisolone	86,000	Exitus	-
3	68	Female	Petechia	8	4,000	Diabetes	Prednisolone	239,000	Complete response	4
4	39	Female	Petechia	24	22,000	No	Prednisolone	312,000	Complete response	5
5	55	Male	Hematuria	10	29,000	Hypothyroidism	Prednisolone	156,000	Complete response	6
6	71	Male	Hemoptysis	6	8,000	Hypertension, LVH	Methyl-prednisolone	27,000	Exitus	-
7	65	Female	Asymptomatic	20	33,000	Diabetes, hypothyroidism	Prednisolone	362,000	Complete response	3
8	33	Female	Asymptomatic	15	19,000	Vertigo	Prednisolone	263,000	Complete response	10
9	63	Male	Petechia	6	36,000	Hypertension	Prednisolone	190,000	Complete response	3
10	44	Female	Petechia	7	11,000	Diabetes, hypertension	Prednisolone	274,000	Complete response	5

Results

A total of 10 patients who met the criteria were reached among the patients who applied to our hospital since the beginning of the pandemic *(Table 1)*. 60% of the patients were female and 40% were male. The mean age of the patients was 60.1. The mean time from the onset of symptoms to the day when thrombocytopenia was detected was 11.9 days. 30% of the patients died while being followed up in intensive care units for COVID-19. Complete response was obtained from 70% of the patients. Hemorrhage was observed in 60% of the patients' physical examination findings. Among these, petechiae with 40% were the most common, followed by asymptomatic 30%, melena 10%, hemoptysis 10%, and hematuria 10%. In 2 patients (20%) with complete response, the diagnosis was made at the time of admission to the internal medicine outpatient clinic after the end of the COVID-19 treatment. The COVID-19 treatment process of these 2 patients did not require hospitalization, there was no lung involvement, and they survived the disease with a mild course. Other patients (80%) had hospitalization. While 3 patients were followed up in 30% COVID-19 intensive care units, 5 50% patients were diagnosed with COVID-19 during hospitalization. Corticosteroid treatment doses were adjusted during discharge for patients who were cured for ITP, and internal diseases polyclinic control was recommended 7 days after discharge. After 7 days, they came to the internal diseases outpatient clinic controls, they were followed up for about 12 months and no recurrence was observed. Organomegaly was not observed in any of the patients (100%). Other patients (80%) had hospitalization. One patient (10%) with melena developed a need for erythrocyte suspension, other patients did not have life-threatening hemorrhage. Three patients with exitus COVID-19 were followed up in the intensive care unit, and their platelet counts (mean 8,600 10^3/uL) were found to be very low. Since the final platelet counts of the patients with exitus did not exceed 100,000 10^3/uL, response evaluation could not be performed. Initially, no platelet clumps or giant platelets were seen in the peripheral blood smears of the patients. No schistocyte with signs of hemolysis was observed, and no atypical cells were observed *(Figure 1)*. All peripheral blood smears were examined and reported by internal medicine specialists. Daily hemogram and peripheral blood smears were followed up from the patients who were hospitalized in the COVID-19 service and intensive care units and were evaluated and

followed up daily by internal medicine specialists.

IVIG was not given to any of the patients. Out of 3 patients (30%) who died, 2 patients (20%) died due to complications related to acute renal failure, and 1 patient (10%) died due to multiorgan failure. The initial platelet counts of patients with exitus at hospital admission were observed to be very low, with an average of 8,600 10^3/uL. Cure was achieved in 7 patients (70%). The platelet count detected at the baseline was the lowest 1,000 10^3/uL, the highest 36,000 10^3/uL, and the mean 18,000 10^3/uL.

The mean platelet counts after treatment were 19,500 10^3/uL. The most common comorbid diseases were hypertension with 30%, diabetes mellitus 23%, hypothyroidism 15%, dementia 7.5%, vertigo 7.5%, cerebrovascular disease 7.5%. 30% of the patients were vaccinated. The mean time passed after vaccination was 2 months, and the rate of unvaccinated patients was 70%. However, it was observed that all unvaccinated patients were diagnosed before the vaccination program was started. It was observed that 5 patients (50%) were given prednisolone, 3 patients (30%) methylprednisolone and 2 (20%) dexamethasone treatments. No elevation was observed in hemolysis markers (LDH, indirect bilirubin, reticulocyte count etc.) and coagulation markers (INR, prothrombin time, D-dimer etc.) of the patients. Since hemorrhage was observed in 70% of the patients, platelet suspension replacement was performed. When the first and last platelet counts were compared, it was observed that the platelet counts of all patients (100%) increased, and no recurrence was observed in the follow-ups *(Table 2)*.

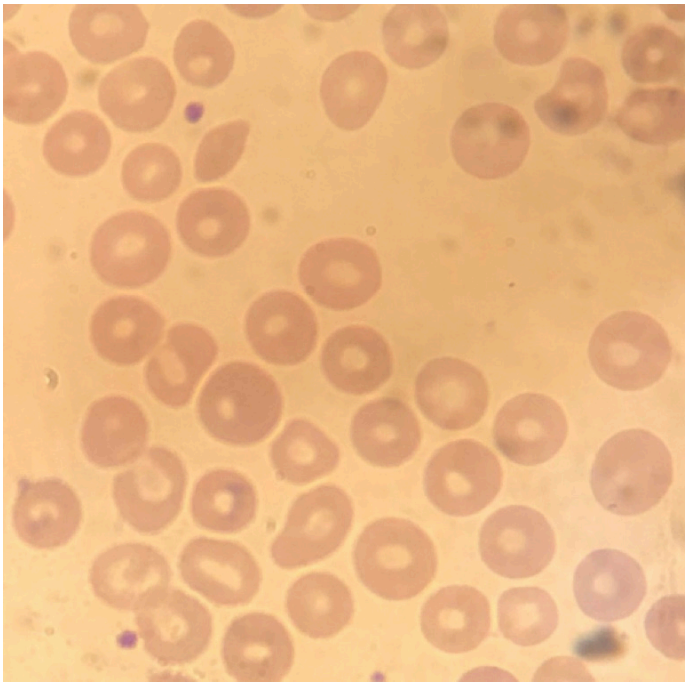

Figure 1. Peripheral smear image of a patient followed for ITP.

Discussion

ITP is a risky condition in the presence of hemorrhage because of its high mortality. In the course of COVID-19 infection, autoimmune diseases such as antiphospholipid syndrome and Guillain-Barré, hematologically COVID-19-related thrombocytopenias, autoimmune hemolytic anemia and immune thrombocytopenias have been described.[10] Our patients were included in the study after excluding other viral agents associated with secondary ITP, drug-related, autoimmune diseases and malignant diseases. Viral infections were excluded because the viral markers sent to the patients were negative. It is thought that viruses cause a decrease in platelet production by infecting megakaryocytes in the bone marrow in the mechanism of thrombocytopenia. This results in apoptosis of megakaryocytes, decreased maturation of megakaryocytes, or decreased expression of the thrombopoietin receptor. Besides, viruses can infect hematopoietic stem cells and cause a reduction of progenitor cells and the induction of growth-deficient megakaryocyte colony forming units due to unregulated production of cytokines by infected cells in the bone marrow. Another suggestion is platelet destruction, where viruses interact directly with platelets or recognize immune complexes of IgGs and viral antigens.[11] Absence of anemia, absence of signs of hemolysis, absence of schistocyte in peripheral blood smear, only low platelet count enabled us to avoid both micro and macroangiopathic hemolytic anemia in the diagnosis. Absence of alarm symptoms (weight loss, night sweats etc.), no mass or organomegaly detected on imaging, and negative tumor markers have led us to stay away from malignant diseases. In

Table 2. Patients' findings.

Prognosis	70% recovery, 30% died
Physical examination signs	40% petechia, 30% asymptomatic, 10% melena, 10% hemoptysis, 10% hematuria
Peripheral blood smear findings	In all of the patients, 100% thrombocyte clusters, schistocytes, and atypical cells were not observed
Comorbid disease	30% hypertension, 23% diabetes mellitus, 1.5% hypothyroidism, 7.5% dementia, 7.5% vertigo, 7.5% cerebrovascular disease
Vaccination rate	30%
Treatments	50% prednisolone, 30% methylprednisolone, 20% dexamethasone

drug-related thrombocytopenia, an increase in thrombocyte count following discontinuation of the drug causes the diagnosis to go away from ITP. Low molecular weight heparin used in thromboembolism prophylaxis, a common complication of COVID-19, causes HIT. Also, some antibiotics used to prevent the development of secondary bacterial infection (ceftriaxone, linezolid, vancomycin etc.) cause drug-related thrombocytopenia. Since there is an autoimmune mechanism in ITP, elevation is not an expected situation. Thrombocytopenia, leukopenia, and hemolytic anemia may develop in cases of hypersplenism such as liver cirrhosis, infiltrative diseases (Gaucher, lymphocytic histiocytosis, infectious mononucleosis etc.), and malignant diseases (leukemia, lymphoma, malignant tumor metastasis etc.). The fact that our patients had a low hematologic series and the absence of hepatosplenomegaly enabled us to avoid the diagnosis of hypersplenism. Peripheral blood smear examination was sufficient to differentiate pseudothrombocytopenia. In summary, after anamnesis, physical examination, and laboratory examinations, no other cause could be found to explain ITP, it was decided that autoimmune thrombocytopenic purpura was present, and steroid treatment was started and followed up. Response to steroids helped support the diagnosis, except in patients with other complications. In order to be called a complete response in the treatment of ITP, the platelet count should double since the start of the treatment or the platelet count should be above 100,000 and the clinical findings should improve.2 According to the American Society of Hematology Association, in the treatment of persistent ITP or chronic ITP, splenectomy, IVIG treatment including rituximab or thrombopoietin receptor antagonist is not recommended.9 On the other hand, we mentioned that the British hematology community recommends IVIG and thrombopoietin receptor antibody (eltrombopag) instead of corticosteroids. Since eltrombopag will take effect in 7-14 days, it should not be preferred in case of emergency bleeding. IVIG treatment, on the other hand, is expensive and has side effects such as fever, arrhythmia, kidney failure, and thrombosis. Since D-dimer elevation and a predisposition to thrombosis are in question in COVID-19 patients, IVIG was not given in the treatment. High-dose corticosteroid therapy was administered to 3 patients in the intensive care unit because they were in the MAS (macrophage activation syndrome). Anti-D treatment, on the other hand, was not preferred in high-risk patients since the response started on the 5th day.

There are various opinions about whether bone marrow aspiration should be performed in patients with ITP. The American Society of Hematology recommended bone marrow aspiration only if there is persistent thrombocytopenia and there is no response to treatment.[12] Since there was no patient among our cases who could not respond to steroid treatment, there was no need for bone marrow aspiration. Recurrence has been shown in patients with ANA positivity or in ITP cases accompanying the course of other autoimmune diseases.[13] The reason for the absence of recurrence in our cases may be considered to be negative autoimmune antibodies.

Conclusions

As clinicians, in suspected cases, secondary causes should be ruled out quickly, ITP diagnosis should be made and steroid treatment should be started. Mostly, cases respond to steroid treatment, but there are options such as IVIG, immunosuppressants, splenectomy in cases that do not respond. In the literature, patients who need advanced treatment in cases of COVID-19-related ITP have been stated. In our study, we think that we contributed to the literature because there was no need for further treatment.

Conflict of interest

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Study Conception, Data Collection and/or Processing, Materials, Literature Review, Manuscript Preparation held by DI.

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