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RESEARCH ARTICLE

Congenital Pulmonary Malformations From The Prenatal to The Postnatal Period: Tertiary Center Experience

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Abstract

Introduction: Our purpose was to review our experience with the fetuses diagnosed prenatally with congenital pulmonary malformations (CPM). **Methods:** Retrospective study of fetuses prenatally diagnosed with congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (BPS), bronchogenic cyst (BC) by ultrasonography between September 2020 and December 2022 **Results:** Sample analysis was based on 34 pregnancies with CPMs. On the basis of prenatal sonographic appearance, CPAM, BPS and BC were identified antenatally in 79.4% (27/34), 14.7% (5/34) and 5.8% (2/34), respectively. Most (76.5%) were isolated, all cases were unilateral (100%) and majority (64.7%) were regressed late antenatally or postnatally with expectant management. Of the 27 fetuses presented with CPAM, postsurgical resection was necessary for 5 cases (18.5%). There was only one case with hydrops and a CPAM volume ratio >1.6 and was managed with thoraco-amniotic shunt prenatally and right lower lobe resection postnatally. Of the 5 fetuses presented with BPS, thoracoscopic excision was necessary for 2 cases. Of the 2 fetuses presented with BC, cyst excision was performed or planned to cases. **Conclusion:** The results from our center in last two years reflect overall favorable outcomes for all CPMs. The role of ultrasound is cost-effective during perinatal period rather than fetal MRI.

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Introduction

Congenital pulmonary malformations (CPM) are a rare group of developmental pulmonary abnormalities that are often first identified prenatally on routine second-trimester ultrasound, including CPAM formally known as congenital cystic adenomatoid malformation, bronchopulmonary sequestration (BPS), congenital lobar overinflation, bronchogenic cyst (BC) and bronchial atresia. Due to widespread availability of prenatal ultrasound combined with the improved resolution of ultrasound technology that enables the detection of smaller lung lesions, the incidence of these malformations is increasing and estimated to be around 1 in 2500 to 8000 live births.[1,2] CPAM and BPS account for a majority of CPMs, while CPAM represents 75% and BPS consists 0.15–6.4% of all congenital lung malformations. Other lesions, such as BCs, are even less common.

CPAM is a developmental malformation of the lower respiratory tract due to failure of maturation of bronchiolar structures during the pseudoglandular stage of lung development, resulting in overgrowth of the terminal bronchioles without corresponding alveoli. The lesion communicates with the tracheobronchial tree and derives its blood supply from the pulmonary arteries. CPAMs can be further categorized into microcystic, macrocystic, or mixed lesions based on prenatal ultrasound (Figure 1-2). BPS is a nonfunctioning lung tissue with anomalous systemic arterial supply that does not communicate with tracheobronchial tree while localised within the normal lung tissue (intralobar) or the development of separate pleura (extralobar) (Figure 2). Hybrid lesions displaying characteristics of CPAM and BPS have been described sonographically and histopathologically. BC is part of the family of foregut duplication cysts, which also includes enteric and neuroenteric cysts and may be located in the mediastinum or in the medial lung parenchyma (Figure 4).

Clinical presentation of CPM is highly variable, ranging from apparent in-utero resolution to even severe mass effect with resultant hydrops fetalis and even fetal demise. Prenatal imaging characteristics on fetal and neonatal outcomes, such as size, appearance (cystic versus solid), mediastinal shift, feeding vessel presence, CPAM-volume ratio (CVR) and hydrops, determine the prenatal and postnatal management strategies.[3,4]

In this study, we describe and evaluate our current experience and to review current literature on the fetuses diagnosed prenatally with the following pulmonary malformations: CPAM, BPS and BC.

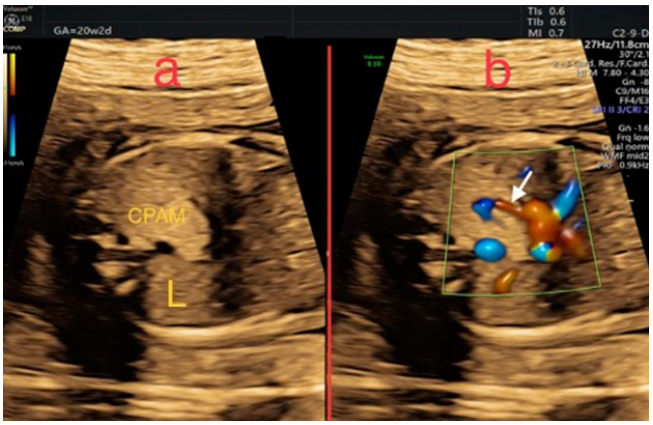

Figure 1. Congenital pulmonary airway malformation (CPAM). a Transverse sonographic image through the fetal chest at 20 weeks of gestation shows a hyperechoic mass (CPAM) and the normal intermediate echogenicity lung parenchyma (L) is visible. b Power Doppler US image of the same image shows a feeding vessel (arrow) from the pulmonary artery supplying the CPAM.

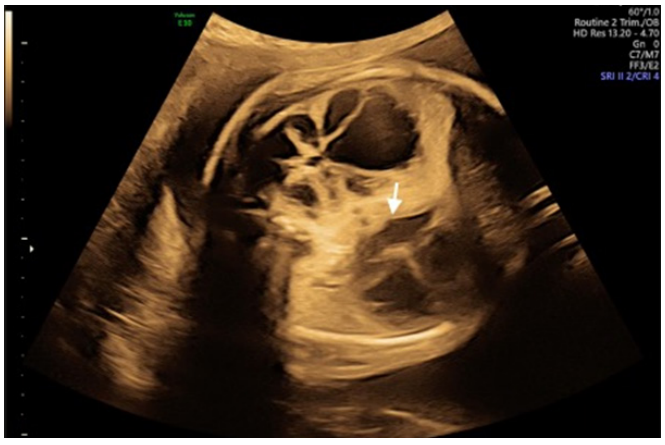

Figure 2. Macrocystic congenital pulmonary airway malformation (CPAM). Transverse sonographic image through the fetal chest demonstrates a multiseptated, primarily anechoic intrathoracic mass (arrow). Cardiomediastinal shift is present, with leftward displacement of the heart.

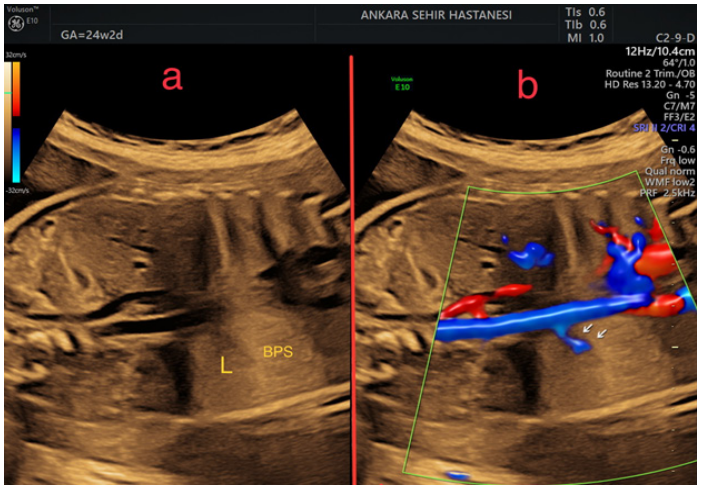

Figure 3 Bronchopulmonary sequestration. a Coronal sonographic image at 24 weeks of gestation shows a hyperechoic wedge-shape mass (BPS) at the posterioinferiorleft lung . The normal intermediate echogenicity lung parenchyma (L) is visible. b Power Doppler US image of the same iamge shows a feeding vessel (arrow) from the descending thoracic aorta supplying the bronchopulmonary sequestration

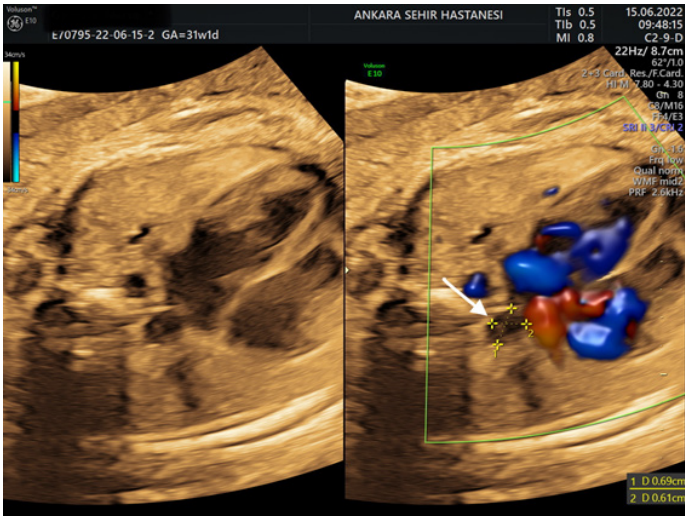

Figure 4. Bronchogenic cyst. Transverse sonographic (left) and transverse color Doppler US image (right) of the same fetus through the fetal chest at 31 weeks. A round, anechoic, avascular cyst (arrow) is present in the midline behind the heart, compatible with a bronchogenic cyst.

Material and Methods

We conducted a review of all pregnancies complicated by a prenatally diagnosed CPAM, BPS, BC at 21-33 weeks of gestation between September, 2020 and December, 2022 in Ankara City Hospital, Department of Obstetrics and Gynecology, Division of Perinatology, Ankara, Turkey. Approval was granted by the local Institutional Review Board for this retrospective cohort study (E2-23-3952). Freely-given informed consent to participate in the study was obtained from all participant pregnant women. Literature search was also carried out to compare our data with those of previous series.

Pregnancies with additional anomalies that could impair lung capacity (e.g. congenital diaphragmatic hernia) were excluded, and subdiaphragmatic BS and esophageal duplication cysts were also excluded since our aim was to investigate the effect of only pulmonary lesions in thorax on perinatal outcomes.

Baseline maternal demographic information and clinical data were obtained from review of stored electronic medical records. Imaging records for all cases were assessed to confirm diagnosis and to calculate the CVR value of cases without records. CVR was calculated by multiplying the three dimensions of the lung mass with 0.52 and dividing by the head circumference according to previously published formula.[3] Thirteen cases for which no or insufficient images had been stored were excluded from the cohort. To perform this study, the following variables were evaluated: Maternal age, gravidity, parity, previous miscarriage, living child, gestational week at diagnosis, location of lesion, initial CVR values, whether the presence of ascites, pleural effusion, hydrops, mediastinal shift and associated structural/chromosomal abnormalities, gestational age at delivery, gender of neonates, birth weight, Apgar scores at first and fifth minutes, NICU admission, mortality due to pulmonary lesion and short term (postnatal first three months) outcome.

The data were collected using an Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA). For statistical analysis, continuous variables were presented as mean& standard deviation (SD) or median and range values according to the normally distributed by using the Kolmogorov–Smirnov test. Categorical variables were expressed as numbers and percentages.

Results

During the study period, 41 pregnancies were evaluated and distribution of congenital thoracal lesions and flowchart illustrating study population selection is presented in Figure 5. Of 41 pregnancies complicated by fetal congenital

thoracal lesions during the study period, 6 cases were excluded from further analysis: three with a coexistent congenital diaphragmatic hernia, two subdiaphragmatic sequestrations, one esophageal duplication cysts, since our aim was to investigate the effect of pulmonary lesions on perinatal outcomes alone. Actually, there were 3 cases with BC, but preliminary diagnosed case was seen as an esophageal duplication cyst during surgical excision and died due to postoperative infection, so it was excluded. Finally, we included 34 cases in the study analysis. According to prenatal sonographic data, 27.5% of cases were microcystic, 31% were macrocystic and 41% of cases were unspecified.

Demographics and characteristics of the study population is presented in Table 1. Maternal mean standard deviation (SD) age was 29.41±4.88 and mean SD gestational week at diagnosis of the pulmonary lesions were 25.03±3.4. Ten of thirty-four pregnant women (29.4%) had maternal disease and/or obstetric complication and all of those except one were present in patients diagnosed with CPAM. There were two cases of twin pregnancy (1dichorionic-diamniotic, 1monochorionic-diamniotic) and in both, only one of the fetuses had CPAM. In both twin pregnancies, fetuses had macrocystic CPAM and were born at 32nd and 34th gestational week. Both newborns underwent thoracic surgery in the first three months postnatally and the prenatal diagnosis was confirmed pathologically. Table 1 outlines the characteristics of the lesions on the basis of prenatal sonographic appearance. Fourteen fetuses (41%) had right- sided lesions, 18 (53%) had left-sided lesions, and 2 fetus (those with BCs) had median

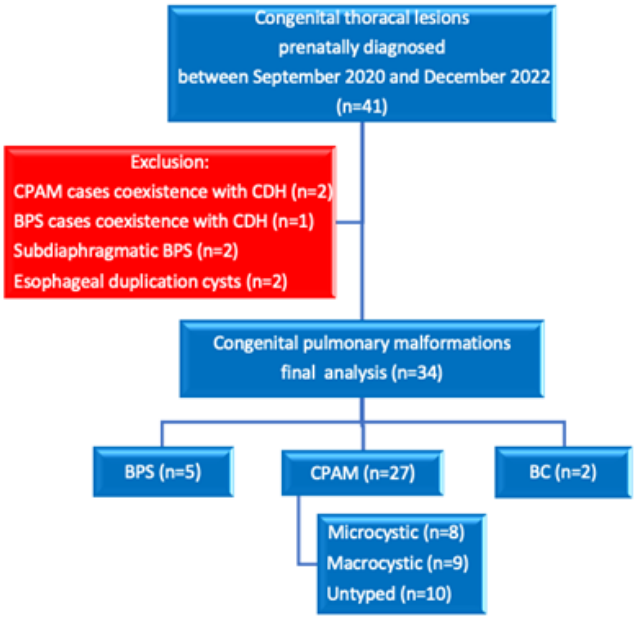

Figure 5. Flowchart illustrating study population selection

Table 1. Demographics and characteristics of congenital pulmonary lesions

	All (n=34)	CPAM (n=27)	BPS (n=5)	BC (n=2)
Maternal age (mean, SD)	29.41±4.88	28.5 ±4.6	33.8 ±5.1	29,31
Gravidity (median, min-max)	2 (1-6)	2 (1-4)	3 (2-6)	2,1
Parity (median, min-max)	1 (0-4)	1 (0-3)	2 (1-4)	0,0
Previous miscarriage (median, min-max)	0 (0-3)	0 (0-1)	0 (0-3)	1,0
Living Child (median, min-max)	1 (0-3)	1 (0-3)	2 (1-3)	0,0
GW at diagnosis (mean, SD)	25.03±3.4	25.04 ±3.4	23.2 ±2.1	28,31
Maternal disease and/or obstetric complication	10/34 (29.4%)	10/27 (37%) 3 GDM 1 GDM+MKDA+PTB 1 asthma 1 placenta previa 1 DKDA+ cerclage 1 GHT 1 hypothyroidism 1 hx of gastric bypass	1/5 (20%) 1 GDM	0
Location of lesion (n, %)				
Right Lung	14/34 (41%)	14/27 (52%)	0/5 (0%)	-
Left Lung	18/34 (53%)	13/27 (48%)	5/5 (100%)	-
Median	2/34 (6%)	-	-	2/2 (100%)
Initial CVR	0.39±0.37	0.39±0.4	0.42±0.17	
CVR>1.6	1/34	1/27	0/5	
Ascites& Hydrops	1/34	1/27	0/5	0/2
Pleural effusion	4/34	4/27	0/5	0/2
Mediastinal shift	8/34	7/27	1/5	
Associated structural and/or chromosomal anomalies	8/34 (23.5%)	6/27 (22.2%) 1 umbilical vein varix 1 single umbilical a. 1IUGR+oligohydramnios 2 polyhydramnios 1 VSD	0/5	2/2 (100%) 1polihidramnios 1DORV+EDC

CPAM: Congenital Pulmonary Airway Malformation; BPS: Bronchopulmonary Sequestration; BC: Bronchopulmonary Cyst; CVR: CPAM Volume Ratio; DORV: Double Outlet Right Ventricle; EDC: Esophageal Duplication Cyst; n: Number; SD: Standard Deviation; MKDA: Monochorionic Diamniotic Twin pregnancy; PTB: Risk of Preterm Birth; DKDA: Dichorionic Diamniotic Twin Pregnancy; GHT: Gestational Hypertension; IUGR: Intrauterine Growth Retardation; VSD: Ventricular Septal Defect; GW: Gestational Week.

lesions identified. In subgroup analysis, we identified that CPAM lesions were predominantly in right lung (52%) and all BPS lesions were in left lung (100%). The mean CVR at initial diagnosis, available in all CPAM and BPS cases, was 0.39 (± SD of 0.37, range 0.04-1.62). Mediastinal shift was evident in 8 of 34 cases. In our cohort, hydrops was identified only in one case; a right-sided microcystic CPAM with ascites, subcutaneous edema, bilateral pleural effusion, mediastinal shift and elevated CVR (1.62). This female fetus underwent placement of thoraco-amniotic shunt at 32th week subsequently resolved and were delivered at 38th week weighing 2020 gr and underwent right lower lobectomy. Histopathological analysis of the resected lobe identified features of macrocystic CPAM. Eight of all 34 cases (23.5%) had other structural anomalies while none of cases with BPS had additional structural anomalies. Six of twenty-seven cases with CPAM (22.2%) had associated anomalies (umbilical vein varix, single umbilical artery, VSD, polyhydramnios and intrauterine growth retardation).

The two cases with BC had other structural anomalies (1 case with double outlet right ventricle and esophageal duplication cyst, 1 case with polyhydramnios). BC case with polyhydramnios was underwent surgical resection and BC with DORV+EDC is still in follow-up, and she is waiting for simultaneous resection with DORV surgery at postnatal 6th month. Actually, there were 3 cases diagnosed with BC and preliminary diagnosed BC case was seen as esophageal duplication cyst during surgical excision.

Only a small minority of cases underwent genetic amniocentesis (n = 4) and all of which returned normal karyotypes.

Table 2 outlines the fetal and neonatal outcomes of congenital pulmonary lesions. None of the pregnancies underwent termination and all thirty-four (100%) of fetuses survived. Most cases were delivered at term, median gestational week at delivery was 38 (range, 32-40) and mean standard deviation (SD) birthweight was 3165±530 gr. Eight of thirty-four neonates (23.5%) were admitted to the NICU following delivery based on local generalized practice irrespective of respiratory status. Majority of congenital pulmonary lesions (64.7%) were resolved late antenatally or postnatally with expectant management. Surgery was performed in 8 of 34 cases (23.55%) and 4 of 34 (11.8%) cases are still being followed. Survival rate in the first three months of neonatal period was 100%.

Discussion

In consistent with the previously and recently published literature, our experience further confirms that CPMs are with benign outcome, which is not usually associated with structural, chromosomal or fetal growth defects.[5-6-7] This study demonstrated that with careful follow-up during pregnancy and after birth, the majority of the pregnancies with congenital pulmonary malformations were delivered at term, without NICU admission, with only 11% need for thoracic surgery during the first 3 months of life. Consequently, survival rate in the first three months of neonatal period was 100%, even in complicated cases with hydrops.

Since most of our cases resolved spontaneously (64.7%), pathological confirmation was only possible in patients who underwent thoracic surgery. However, thanks to the ultrasonographic improvements, all of the postnatal computed tomography performed in the postnatal period were concordant with our prenatal diagnoses, except for two case. In one of the three fetuses followed up prenatally with BC, esophageal duplication cyst was seen on gross examination during surgical excision, and we excluded this case from our study. The other discordant case was confirmed as CPAM postnatally, which we diagnosed as hybrid lesion prenatally. Despite antenatal diagnosis of congenital cystic lung lesions

Table 2. Fetal and neonatal outcomes of congenital pulmonary lesions

	All (n=34)	CPAM (n=27)	BPS (n=5)	BC (n=2)
Termination of pregnancy	0	0	0	0
Fetal thoraco-amniotic shunt procedure	1/34	1/27	0	0
GA at delivery (median, min-max)	38 (32-40)	39(32-40)	38(37-40)	36, 39
Birthweight (gram, mean, SD)	3165±530	3138±530	3421±349	2470, 3320
Gender (n, %)				
Male	18 (53%)	15 (55%)	3 (60%)	
Female	16 (47%)	12 (45%)	2 (40%)	2/2 (100%)
Apgar at 1st minute (median, min-max)	7 (5-7)	7 (5-8)	7 (7-7)	7,9
Apgar at 5th minute (median, min-max)	9 (7-9)	9 (7-9)	9 (8-9)	7,9
5th minute Apgar < 7	0	0	0	0
NICU admission (n, %)	8/34 (23.5%)	6/27 (22.2%)	1/5 (20%)	1/2 (50%)
Short term outcome (n, %)				
Spontaneous resolution	22/34 (64.7%)	19/27 (70.4%)	3/5 (60%)	0/2
Expectant management	4 /34 (11.8%)	3/27 (11.1%)	0/5 (0%)	0/2
Thoracic Surgery	8/34 (23.55)	5/27 (18.5%)	2/5 (40%)	1/2
Planned for surgery				1/2
Mortality due to pulmonary lesion	0 (0%)	0 (0%)	0 (0%)	0 (0%)

CPAM: Congenital Pulmonary Airway Malformation; BPS: Bronchopulmonary Sequestration; BC: Bronchopulmonary Cyst; NICU: Neonatal Intensive Care Unit; GA: Gestational Age

reaches 85.7% due to sonographic improvements,8 the ultrasonographic appearance of CPMs in our study was indistinguishable as reported before and only color Doppler ultrasound made the definition between CPAM and BPS demonstrating their unique and different blood supply.[9] Prenatal magnetic resonance imaging (MRI) was reported to have high sensitivity and specificity in the detection of pulmonary lesions and consistent with surgical pathology in 82–91% of cases while this consistence was 82-83% by ultrasonography. However, as it appears more cost-effective that prenatal management and prognostication based on lesion size than prediction based on suspected final histology, MRI did not demonstrate any added value in terms of diagnosis and prognosis compared to the ultrasound.[10],[11] As previously reported that the prognosis of CPMs was associated with elevated CVR, mediastinal shift and presence of hydrops fetalis, also supports the cost-effectiveness of ultrasound in prenatal diagnosis [3],[12] Supporting the literature, we had the only one case with elevated CVR (1.62), and that was the only case who developed hydrops. Fetal management was carried out by placement of a thoraco-amniotic shunt.

Literature about thoraco-amniotic shunt placement reported periprocedural complications including premature preterm rupture of membranes (PPROM), preterm labor, chorioamnionitis, shunt occlusion, and fetal dislodging of the shunt requiring a new shunt placement with the same risks, and postnatal complications including rib deformities in 77% of the neonates.[13],[14] Fortunately, although our case was complicated with IUGR and oligohydramios, she was delivered at 38th gestational week without periprocedural complications.

The surgical management in neonates and infants with CLMs is consensual for symptomatic patients while postnatal management of asymptomatic patients is controversial. Some propose prophylactic surgery in the asymptomatic infant to avoid possible infection and malignancy that could develop later in life.[15],[16] However, some clinicians recommend for conservative management of asymptomatic prenatally CPAMs and BPSs.[16] In a meta-analysis of 1,070 neonates with CPAM and BPS, approximately 50% remained asymptomatic into infancy, and only 3% of the asymptomatic infants eventually became symptomatic while being observed or awaiting for surgery.[17] Our clinicians applied expectant management in asymptomatic cases, as highlighted in table 2, surgery was performed in 23.5% of all cases.

Congenital pulmonary malformations could be associated with other congenital malformations. Associated abnormalities seen in 3-12% of CPAMs and those present up to 50% of BPSs.[18] However, it is noteworthy that in our study, no associated abnormalities were observed in any of the 4 BPSs cases.

Our study has some limitations. The main limitations were retrospective design and the lack of long-term outcomes. Additionally, the impact of corticosteroids as therapy on the perinatal outcomes of fetal CPMs could not be assessed, as this information was not readily available. It may depend on the fact that it is used according to the initiative of the physician. It is not included in the routine protocols in our clinic as it cannot be proven due to small sample sizes. Finally, histopathological diagnosis was only available in a minority of cases due to local preference for conservative management and the high spontaneous resolution rates of lesions.

Conclusion

The findings from our center in last two years reflect overall favorable outcomes for all congenital pulmonary malformations, even in complicated cases with appropriate management. The role of ultrasound in the diagnosis and management of congenital pulmonary malformations is important and cost-effective during perinatal period rather than fetal MRI and other diagnostic tools. However, esophageal duplication cysts should be taken into consideration in the differential diagnosis of cases prenatally diagnosed with BC by ultrasonography. Serial ultrasounds should be performed to evaluate the malformation, to assess the fetus for associated anomalies and to plan for delivery and future treatment. Although the vast majority regressed spontaneously, a multi-disciplinary team should play a vital role in ensuring that the mother and fetus receive current and recommended treatment and are managed antenatally and postnatally. Even in asymptomatic cases, or those with ultrasounds suggestive of a regressed lesion, they should still undergo investigation with a postnatal follow-up because of the risk of long-term sequelae and malignancy.

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Conficts of Interests

The authors have no relevant financial or non-financial interests to disclose.

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Data Availability Statement

Data available on request due to privacy/ethical restrictions. The data used in this study can be shared on demand if any concern rises due to the reliability of the data but according to the ethical and legal regulations in Turkey the authors can not share the data via a data repository.

Authors contributions

All authors contributed to the study conception and design and meet the ICMJE criteria for authorship. Material preparation, data collection, study design and analysis were performed by [Aysegul Atalay]. The first draft of the manuscript was written by [Aysegul Atalay]. [Dilek Sahin] critically revised and commented on previous versions of the manuscript and study supervision. All authors read and approved the final manuscript.

Ethical approval

Ethics approval was obtained from the institutional review board. The study was conducted in accordance with the Declaration of Helsinki.

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RESEARCH ARTICLE

Inpatient follow-up in the palliative care center or the cardiology clinic in patients with end-stage heart failure? cost-effectiveness study, two-center retrospective study

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Abstract

Introduction: The aim of this study is to compare the treatment costs, hospitality costs and total costs of the patients who were hospitalized for chronic decompensated heart failure and monitored by the Palliative Care Center and Cardiology Clinic during a one-time hospitalization. **Methods:** A two-center retrospective study was performed. A total of 92 patients were included in this study. Thirty-eight out of the 92 were inpatients with chronic decompensated heart failure, and were monitored in the Palliative Care Center, and the other 54 were dealing with chronic decompensated heart failure and were treated at the Cardiology Clinic. **Results:** At the end of the day, 42.10% of the patients hospitalized in the Palliative Care Center and 37.03% of the patients hospitalized in the Cardiology Clinic were women. The mean age of the patients hospitalized in the Palliative Care Center was 76.71 ± 11.34 years; the mean age of the patients hospitalized in the Cardiology Clinic was 74.09 ± 11.16 years. There was no statistical difference between the two groups. The duration of hospitalization for patients in the Palliative Care Center was longer than patients in the Cardiology Clinic. The cost to the patient was greater in the palliative care center in terms of the average cost of treatment per patient, average cost of hospitality management and average total cost per patient, which was statistically important ($p < 0.05$). The mortality rate that was observed during hospitalization was lower in the Cardiology Clinic by a statistically important margin ($p < 0.05$). **Conclusion:** The cost of treatment, the cost of hospitality and the total cost of hospitalization for chronic decompensated heart failure patients were higher in the Palliative Care Center than in the Cardiology Clinic. However, it was observed that the rate of mortalityand higer co-morbidities in the Palliative Care Center was higher than the Cardiology Clinic.

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Introduction

Palliative care is a type of specialized medical care for patients living with a serious chronic illness. Such care aims to reduce patient discomfort, improve quality of life and minimize stress. Although palliative care was initially implemented to alleviate the suffering of cancer patients at the end of their lives, today it aims to help patients and their caregivers adapt to the new reality at an earlier stage in diseases that may end up being fatal.[1] In addition to cancer patients, palliative care services also provide services to patients with heart disease, stroke, muscle and nerve diseases that have caused lesion and dysfunction, end-stage liver disease, end-stage renal failure, Alzheimer's disease and dementia, chronic lung disease, Parkinson's disease, congenital disease, and other chronic diseases that result in limitation of movement or bed dependency.

Studies show that palliative care is effective in both reducing symptom burden and improving quality of life. It has also shown to be cost-effective and is synonymous with quality of care.[2]

Heart failure is a chronic and progressive disease prevalent in approximately12% of those 65 years and older around the world, and this rate tends to increase each year.[3] Heart failure is a major health problem due to its high morbidity and mortality rates, as well as bringing symptoms that lead to a poor quality of life.[4] Patients living with heart failure often struggle with many conditions including dyspnea, orthopnea, and often uncontrollable symptoms such as edema and fatigue, depression, anxiety, and psychosocial stress.

However, palliative care may offer some benefits to those dealing with heart failure, such as a focus on reducing symptom burden, improvement in mental health, and reduction in the overall number of hospital admissions. At the same time, it can help promote a successful environment for home-care, as it also deals with relatives watching over patients with heart failure.[5]

Both the World Health Organization (WHO) and the European Society of Cardiology agree that it is necessary to work alongside palliative care not only for end-stage heart failure patients, but also from the moment of diagnosis of heart failure.[6,7] Despite this, the number of patients who can receive palliative care is very limited among patients struggling with heart failure in Türkiye as in the whole world.

Since heart failure patients are in the category of those requiring multiple hospitalizations, patient-based cost rates can be quite high. There are few studies on this subject and the results are inconsistent.

In this retrospective two-center study, we aimed to compare the treatment costs, hotel costs, and total costs of patients hospitalized for chronic decompensated heart failure who were followed up by the Palliative Care Center and the Cardiology Clinic during a single hospitalization.

Material and Methods

A two-center retrospective study was designed. Since there was no coronary angiography unit in the Cardiology Clinic, coronary angiography, coronary balloon-stent, artificial heart pump, and artificial heart assist devices were not utilized. Patients over 18 years of age, struggling with chronic decompensated heart failure and receiving inpatient treatment at the Palliative Care Center, and patients receiving inpatient treatment at the Cardiology Clinic who were demographically similar were included in the study. Patients younger than 18 years of age, pregnant women, patients with postpartum cardiomyopathy, acute myocardial infarction, acute myocarditis, isolated right heart failure, and isolated diastolic heart failure were excluded. Patients were consecutively included according to the date of hospitalization. Transthoracic echocardiography was performed to evaluate cardiac function before hospitalization. Patients with a left ventricular ejection fraction of 50% or less were also included in the study. The left ventricular ejection fraction was calculated using Simpson's method. The principles of the Declaration of Helsinki were followed throughout this study. Patient data were obtained from the data processing-automation center and billing unit of Ankara City Hospital and Health Sciences University Darıca Farabi Training and Research Hospital after obtaining ethics committee approval.

Local ethics committee approval was obtained from the Ankara City Hospital Ethics Committee 1 with the date 20/01/2021 and number E1-21-1158.

Statistical Analysis

Demographic data and baseline characteristics of all patients were summarized. All continuous variables were described using descriptive statistics, including the number of observations (N), mean, standard deviation (SD), median, minimum and maximum. All categorical variables were summarized using the number and percentage of subjects. Demographic data and treatments of the patients

in the two groups were statistically compared. Normality for variables was tested with the Shapiro-Wilk test using Q-Q plots and histograms. Differences between variables were assessed using the Independent two-sample t-test or Mann-Whitney-U test, depending on normality, while the Chi-square test ($\chi 2$) was used for categorical values. Statistical analyses were performed using SPSS version 26 (IBM Corp., IBM SPSS Statistics for Windows, Version 26.0. Armonk, New York: IBM Corp).

Results

A total of 92 patients were included in the study, consisting of 38 chronic decompensated heart failure patients who were monitored as inpatients by the Palliative Care Center of Ankara City Hospital from 01/2020 to 01/2021 and 54 chronic decompensated heart failure patients who were monitored as inpatients by the Cardiology Clinic of Health Sciences University Darıca Farabi Training and Research Hospital. Thirty-six (39.10%) of the patients included in the study, 16 (42.10%) of the patients hospitalized in the Palliative Care Center and 20 (37.03%) of the patients hospitalized in the Cardiology Clinic were women. When the two groups were compared in terms of gender, it was determined that there was no statistical difference (p=0.20). The mean age of the patients included in the study was 75.17±11.25 years. The mean age of the patients hospitalized in the Palliative Care Center was 76.71 ± 11.34 years; the mean age of the patients hospitalized in the Cardiology Clinic was 74.09 ± 11.16 years. When the patients in these two groups were collation terms of age, there was no statistical difference (p= 0.20). The mean length of hospitalization of the patients contain in the study was 12.22±9.69 days. The mean length of stay of the patients was 14.89±10 days in the Palliative Care Center and 10.35±9.07 days in the Cardiology Clinic. When the two groups were collation in terms of length of stay, it was determined that the patients were hospitalized longer in the Palliative Care Center, and there was a statistical difference (p<0.05). During hospitalization, there was exitus in 21 percent (22,80%) of the patients. The mortality rate observed during hospitalization was 34.21% in the Palliative Care Center and 14.81% in the Cardiology Clinic. When the mortality of the two groups was compared, the rate was lower in the Cardiology Clinic and this was statistically important (p < 0.05). Demographic data of the patients including age, gender, length of hospitalization, and comorbidities are given in Table 1. It was determined that patients hospitalized in the Cardiology Clinic received more positive inotropic support as well as new oral anticoagulants, oral nutrition, and total parenteral nutrition support than patients hospitalized in the Palliative Care Center. It was found that patients hospitalized in the Palliative Care Station also received aspirin, clopidogrel, and low molecular weight Heparin treatment more frequently than patients hospitalized in the Cardiology Clinic. The medications used by the patients are given in Table 2. The average treatment cost per patient in the Palliative Care Station was 2140.46 TL (min 1229.00 TL - max 6631.72 TL) (292.41 $ [min 167.89$-max 905.97$]), while the average treatment cost per patient in the Cardiology Clinic was 773.43 TL (min 71.00 TL - max 4564.73 TL) and the cost in dollars was $105.65 (min $105.89 - max $623.49). When these two groups were compared in terms of the average treatment cost per patient, the average treatment cost was higher in the Palliative Care Center and this was statistically significant (p<0.05). The average hospitality cost per patient in the Palliative Care Center was 8173.73 TL ($1116.62) (min 150.00 TL [$20.49] - max 68496.25

Table 1. Demographic data of the patients including age, gender, length of hospitalization, and comorbidities

Variables	Patients in the Palliative Care Center s (%) 38 (41,30)	Inpatients in the Cardiology Clinic S (%) 54 (58,70)	Total patients s=92	p
Female gender s (%)	16 (42,10)	20 (37,03)	36 (39,10)	>0,05
Age (year)	76,71±11,34	74,09±11,16	75,17±11,25	0,20
Length of hospitalization (days)	14,89±10	10,35±9	12,22±9,69	<0,05
Alzheimer's disease s (%)	20 (52,63)	4 (7,40)	24 (26,10)	<0,05
Cancer s (%)	16 (42,10)	2 (3,70)	18 (19,60)	<0,05
Diabetes mellitus s (%)	13 (34,21)	16 (29,62)	29 (31,50)	0,06
Hypertension s (%)	19 (50,00)	29 (53,70)	48 (52,20)	0.08
CAD s (%)	15 (39,47)	20 (37,03)	35 (38,00)	<0,05
COPD s (%)	8 (21,05)	6 (11,11)	14 (15,20)	0.06
CRF s (%)	22 (57,89)	37 (68,51)	59 (64,10)	0.20
Hemodialysis s (%)	13 (34,21)	13 (24,07)	26 (28,30)	0.20
Ejection fraction %	30 (20-50)	30 (20-50)	30 (20-50)	0,70
Discharged to home s (%)	22 (57,89)	45 (83,33)	67 (72,80)	<0,05
Transfer to intensive care unit s (%)	1 (2,63)	0	1(1,10)	
Discharge to care home s (%)	2 (5,26)	1 (1,85)	3 (3,30)	0,7
Exitus s (%)	13 (34,21)	8 (14,81)	21 (22,80)	<0,05

S: Number , CAD: Coronary Artery Disease , COPD: Chronic Obstructive Pulmonary Disease , CRF: Chronic Renal ailure

TL [$9357.41]), while the average hospitality cost per patient in the Cardiology Clinic was 4031.87 TL ($550.80) (min 372.00 TL [$50.81] - max 27300.00 TL [$3729.50]). When the two groups were compared in terms of the average hospitality cost per patient, the average hospitality cost was higher in the Palliative Care Center and this was statistically important ($p<0.05$). The mean total cost per patient in the Palliative Care Center was 10314.20 TL ($1409.04) (min 1229.11 TL [$167.89] - max 73461.00 TL [$100035.65]), while the mean total cost per patient in the Cardiology Clinic was 4785.82 TL ($653.68) (min 653.46 TL [$89.27] - max 28636.0 TL [$3912.02]). When the two groups were collation in terms of the mean total cost per patient, the mean total cost was higher in the Palliative Care Center and this was statistically important ($p<0.05$).

Table 2. The medications used by the patients

Variables	Patients in the Palliative Care Center s (%) 38 (41,30)	Inpatients in the Cardiology Clinic s (%) 54 (58,70)	Total patients s (%) 92(%100)	p
ACE Inhibitor/ARB s (%)	9 (23,68)	19 (35,18)	28 (30,40)	0,20
Beta blocker s (%)	27 (71,05)	37 (68,51)	64 (69,60)	0,70
Digoxin s (%)	10 (26,31)	20 (37,03)	30 (32,60)	0,20
CCB s (%)	26 (68,42)	45 (83,33)	71 (77,20)	0,09
Positive inotrope s (%)	16 (42,10)	27 (50,00)	43 (46,70)	<0,05
NOAC s (%)	7 (18,42)	27 (50,00)	34 (37,00)	<0,05
Aspirin/clopidogrel s (%)	28 (73,68)	18 (33,33)	46 (50,00)	<0,05
Varfarin s (%)	2 (5,26)	7 (12,96)	9 (9,80)	0,20
Furosemid s (%)	29 (76,31)	40 (74,07)	69 (75,00)	0.80
Spirinolactone s (%)	25 (65,78)	37 (68,51)	62 (67,40)	0.70
LMWH s (%)	28 (73,68)	19 (35,18)	47 (51,10)	<0,05
Oral nutritional support s %	20 (52,63)	45 (83,33)	65 (75,70)	0,70
NG/PEG s (%)	16 (42,10)	1 (1,84)	17 (18,50)	<0,05
TPN s (%)	2 (5,26)	8 (14,81)	10 (10,90)	<0,05

ACE Inhibitor: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker, NOAC: novel oral anti-coagulant, LMWH: low molecular weight Heparin, NG: nasogastric, PEG: percutaneous endoscopic gastrostomy

Discussion

Early palliative care in heart failure patients offers many advantages, such as symptom management, prevention of depression, improvement of grade of life, and alleviation of the burden of family members providing care, but the effects of palliative care on recurrent hospitalizations and cost-effectiveness are still unclear. As far as we were able to investigate, there is no multicenter study on cost analysis in inpatients for our country.

In this retrospective two-center study, there was no important difference in the mean age of patients receiving palliative care compared to the patients receiving classical inpatient care. It was observed that patients in both groups were in the geriatric age group. That appears consistent with the literature.[8]

When co-morbidities such as diabetes, hypertension, COPD, and chronic renal failure were examined in our study, no important difference was sight between heart failure patients receiving conventional treatment and heart failure patients receiving inpatient treatment in a palliative care center. However, the presence of active cancer and basic palliative care indications such as Alzheimer's disease and previous cerebrovascular events were significantly higher in the group of patients followed up in palliative care centers. This may have been due to the palliative care center consultations of the clinician who followed the patient before palliative care, as patients with cancer and co-morbidities such as cerebrovascular diseases and Alzheimer's disease were matched with the need for palliative care because they had a more indigent patient profile.

It was observed that most of the nutrition was provided by oral route in both groups. Studies suggest that to improve the quality of life in patients with poly-morbidity, the functional gastrointestinal tract should be monitored and supplemented with enteral products in cases of inadequate oral nutrition.[9,10] In addition to health hazards relating to dietary salt restriction and obesity, many nutritional problems such as cardiac cachexia and sarcopenia may develop in heart failure patients that should be taken into consideration.[11] It was observed that tube feeding was important higher in patients with heart failure who were followed up in a palliative care center. This may be due to the high prevalence of dysphagia in patients with Alzheimer's disease and cerebrovascular disease. Malnutrition occurs as a result of inadequate intake of daily nutrients. Its negative effects on the length of stay in all inpatients are well known. Malnutrition, also known as cardiac cachexia, has been detected in up to 40% of inpatients with chronic heart failure.[12] Many factors can have an impact on malnutrition in patients with heart failure, including old age, intestinal edema, anorexia triggered by inflammation, nausea, and vomiting, low activity of daily living caused by dyspnea, and anxiety. Like all clinicians, cardiologists dealing with heart failure have knowledge of this issue. However, in order to alleviate major morbidity symptoms such as dyspnea and edema in patient, the

fluid-salt restriction is essential and this is one of the factors preventing patients from accessing adequate nutrients. In our study, while over 90% of the patients more than in the palliative care center received nutritional support, this rate did not exceed 30% in the group hospitalized in the classical cardiology service. There is a significant difference between them. There are also significant differences between nutrition methods. Although the effects of oral supplements in eliminating cachexia in patients with heart failure are controversial, all patients in our palliative care center were screened for nutrition under the supervision of a specialist dietician with the goal of providing the level of nutrient consumption considered optimal for our country in a multidisciplinary approach.[13]

Patients with heart failure receive many drug therapies both to manage symptoms and to improve the chances of survival. There was no difference in the use of ACE inhibitors/ARBs, beta-blockers, digoxin, calcium channel blockers, diuretics, spironolactone and other basic medications in heart failure patients followed in palliative care centers compared to cardiology services. However, there was a significant difference between antiaggregant and anticoagulant preferences.

When the patients were evaluated in terms of mortality during hospitalization, it was found to be significantly higher in patients hospitalized in palliative care centers. In a study by Chioncel et al. which included 9428 patients, all causes of killing in patients hospitalized with heart failure were found to be 18.6% per year. Although this rate is similar to the mortality rates in palliative care, it is important higher than the patient population followed by cardiology. This may be due to the fact that our study was cross-sectional and included single hospitalizations of patients.[14]

Heart failure is an increasing clinical and economic burden in the United States. Robust cost data on disease burden are critical to inform economic evaluations of new therapeutic interventions.[15] One of the aim of palliative care is actually the use of cost-effective health management. There are limited studies showing that palliative care is more effective in patients with heart failure.[16] However, there is no clear proof that it reduces readmissions.[17]

In our study conducted in two different tertiary centers, it was detected that the transaction costs of palliative care were higher than the invoices generated as a result of follow-ups in the classical cardiology service. This is due to the differences between the pricing of inpatient services at our social security institution and the service pricing of the palliative care center. Since the social security institution in Türkiye considers palliative care to be a specialty service due to the team being made up of psychologists, spiritual support, physiotherapists, dieticians, specialized nurses, and doctors, as well as specialized hospitality support and care staff, its pricing differs from normal service or primary intensive care pricing. At the same time, this leads to heightened hotel costs in the palliative care station due to the longer lying days compared to the cardiology clinic. Limitations: We had relatively few patients in our study. This is due to the fact that we have 16 beds in our 3rd step hospital with 3500 beds, and unfortunately, we cannot allocate enough beds for patients with heart failure because there are outpatient admissions from all units at the same time, so the number of palliative care patients followed up with heart failure is low.

In conclusion, in this study, we detected that the cost of therapy, hotel costs, and total costs of inpatients with chronic decompensated heart failure were higher in the Palliative Care Center than in the Cardiology Clinic. However, considering the mortality rates in clinics, we think that this is related to the fact that the patient profile in palliative care centers is worse, and therefore, additional treatment and the hotel services are consequently more expensive. Large prospective studies are needed to answer the question of how to follow up end-stage heart failure patients in a cost-effective manner.

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RESEARCH ARTICLE

The Effect of Preservation of the Bladder Neck on Incontinence Rates in Patients Who Undergo Robot-Assisted Laparoscopic Radical Prostatectomy

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Abstract

Introduction: We aimed to compare the postoperative continence rates in prostate cancer patients who had robot-assisted radical prostatectomy (RARP) when bladder necks were "unpreserved", "preserved" and "extremely preserved".
Methods: In this study, the data of 184 patients who underwent RARP for localized prostate cancer in our clinic between August 2019 and January 2023 were analyzed. The patients were divided into three groups as the bladder neck was not preserved (Group 1), the bladder neck was preserved (Group 2), and the bladder neck was extremely preserved (Group 3). Incontinence status was evaluated with the 24-hour pad test postoperatively at the 1st, 3rd 6th month and 12th months.
Results: One month after surgery, the rate of fully continent patients was higher in Group 3 (39.1%) than Groups 1 and 2 (27.5% and 32.7%, respectively), however the difference was not statistically significant (p=0.483). At the postoperative 3rd month, the rate of fully continent patients was 56.5% in Group 3, 51.9% in Group 2 and 43.1% in Group 1 (p=0.361). The rate of patients with moderate incontinence was higher in Group 1 compared to other study groups (p=0.019). The rate of fully continent patients was 82.6% in Group 3, 73.1% in Group 2 and 61.5% in Group 1 at 6th postoperative month (p=0.079). At postoperative 6 month a significant difference was observed for moderate incontinence rates (15.6%, 5.8% and 0 for Groups 1, 2 and 3, respectively) (p=0.034). At the postoperative 12th month, the rate of fully continent patients was 91.3% in Group 3, 80.8% in Group 2 and 72.5% in Group 1 (p=0.118).
Conclusion: Our results indicated that the approaches for preserving the bladder neck during RARP did not have a statistically significant effect on the prevalence of incontinence, however reduced the severity of incontinence.

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Introduction

Radical prostatectomy (RP) is the preferred treatment choice in localised prostate cancer. RP approaches are open radical prostatectomy (ORP), laparoscopic radical prostatectomy (LRP) and robot-assisted radical prostatectomy (RARP); LRP and RARP being minimally invasive approaches. Increasing trend for minimally invasive approaches has also affected RP procedures, and there is a global increase in the number of RARP.[1] It has been shown that RARP and ORP are similar for oncological outcomes, however RARP is superior in terms of perioperative results (complication rate, loss of blood and rate of blood transfusion, hospital stay, and duration of urinary catheterization).[2,3] Although various studies reported that RARP is superior to open surgery in terms of post-prostatectomy incontinence (PPI) rates,4 most of the studies indicate that there is no significant difference between two approaches for PPI.[3,5,6] Significant negative effect of PPI on quality of life have prompted clinicians to study on this issue further, and preoperative factors affecting PPI were defined as age, surgeon experience, hospital volume, prostate size and preoperative urinary function and various surgical techniques [prostatic urethra preservation, neurovascular bundle (NVB) preservation, bladder neck preservation, Retzius sparing RP], and the surgical techniques have been employed to reduce postoperative incontinence rates. Those techniques have particularly been established during RARP applications, thanks to its high mobility and magnification features.[7-9] Various studies showed that bladder neck sparing techniques during RARP increased continence rates without compromising oncological principles.[10]

The aim of this study is to compare the incontinence rates of the patients with unpreserved bladder neck, preserved bladder neck and extremely preserved bladder neck after RARP performed for nonmetastatic prostate cancer.

Material and Methods

Ankara Bilkent City Hospital No. 1 Clinical Research Ethics Committee approved the study protocol (date: 26 April 2023, no: E1-23-3483). The study was conducted in accordance with ethical rules and the principles of the Declaration of Helsinki.

In this study, the data of 184 patients who underwent RARP for localized prostate cancer in our clinic between August 2019 and January 2023 were analyzed retrospectively. The patients who had preoperative urinary incontinence were excluded. Demographic data (comorbidities, age, body mass index), preoperative data (PSA level, Gleason score on biopsy, clinical T stage, D'Amico risk groups), perioperative parameters [duration of surgery, estimated blood loss (EBL), nerve preservation status, whether lymph node dissection was performed and bladder neck preservation status], postoperative parameters (hospital stay, drain removal time, urethral catheter removal time, incontinence) and final histopathology results (pathological T stage, Gleason score, surgical margin positivity, extracapsular spread, invasion of seminal vesicle and positive lymph nodes) and complications of the patients included in the study were recorded. Then, the patients were divided into three groups as "bladder neck unpreserved" (Group 1), "bladder neck preserved" (Group 2), and "bladder neck extremely preserved" (Group 3). The collected data were compared among the study groups.

Surgical Technique

All patients underwent transperitoneal RARP using a four-armed DaVinci robotic surgical system (Intuitive Surgical, Inc., Sunnyvale, CA). In our study, "bladder neck preservation" was defined as careful dissection of the bladder neck and the base of the prostate and a vesico-urethral anastomosis without any need for bladder neck reconstruction, and "extreme bladder neck preservation" was defined as the length of the preserved intraprostatic segment of the bladder neck >1 cm, as described by Dal Moro et al.11 The bladder neck was not preserved in presence of median lobe or in patients with a lesion at the base of the prostate on mpMRI, and vesico-urethral anastomosis was performed by applying bladder neck reconstruction after resection.

Evaluation of Incontinence

Incontinence status was evaluated with 24-hour pad test, and the first evaluation for incontinence was done in the postoperative 1st month. Daily urinary incontinence amount was grouped as mild if it was <100 g, moderate if it was 100–400 gr, and severe if it was >400 g.12 After the first evaluation at the first postoperative month, incontinence was re-evaluated with the 24-hour pad test in postoperative 3rd, 6th and 12th months.

Statistical analysis

All statistical analyses were done with SPSS 20.0 (IBM, Chicago, IL, USA) software. Kolmogo-

rov-Smirnov test was used to test the conformity of the quantitative data to the normal distribution. Since the parametric test assumptions were not met and the data did not fit the normal distribution, the quantitative data were analyzed with Mann Whitney-U test among the groups. Chi-square test was employed to test the qualitative data. Significance was set at $p < 0.05$.

Results

A total of 184 patients; 109 patients in Group 1, 52 patients in Group 2, and 23 patients in Group 3, were included in the study. There was no difference among the groups in terms of comorbidities, BMI, prostate volumes, PSA levels, or mean Gleason scores on biopsy. The groups were similar in terms of clinical T stage and D'Amico risk stratification (Table 1).

Table 1: Demographic, laboratory and pre-operative clinical data of the study groups

	Group 1 (n=109)	Group 2 (n=52)	Group 3 (n=23)	p
	n (%)	n (%)	n (%)	value
Age (years) (min-max)	64.37±6.26 (47-78)	64.1±6.27 (52-76)	61.83±7.63 (42-75)	0.33
BMI (kg/m²)(min-max)	27.66±3.3 (20.6-39.2)	27.02±2.68 (22.5-36.1)	27.8±2.77 (24.3-34.9)	0.44
Prostate volume (cc) (min-max)	49.6±25.5 (10-177)	43.4±15.37 (20-80)	41.5±15.36 (20-80)	0.27
Comorbidities; -ASHD	23(21.1%)	7(13.5%)	3(113%)	0.40
-COPD	3(2.8%)	1(1.9%)	0	0.85
-DM	24 (22%)	10(19.7%)	5(21.7%)	0.98
-HT	47(43.1%)	17 (32.7%)	6(26.1%)	0.20
PSA level (ng/dl)	10.05±7.68 (0.5-49)	8.05±5.43 (1.3-30)	10.56±8.4 (3.36-34)	0.26
Gleason score on biopsy	6.52±0.79 (6-9)	6.52±0.8 (6-9)	6.83±0.98 (6-9)	0.29
Clinical T stage; -T1a	1 (0.9%)	0	0	
-T1b	2 (1.8%)	1 (1.9%)	0	
-T1c	58 (53.2%)	22 (42.3%)	11 (47.8%)	0.07
-T2a	41 (37.6%)	19 (36.5%)	6 (26.1%)	
-T2b	3 (2.8%)	0	2 (8.7%)	
-T2c	4 (3.7%)	10 (19.2%)	4 (17.4%)	
D'Amico classification; -Low risk	47 (43.1%)	26 (50%)	6 (26.1%)	
-Medium risk	40 (36.7%)	12 (23.1%)	8 (34.8%)	0.13
-High risk	22 (20.2%)	14 (26.9%)	9 (39.1%)	

BMI Body Mass İndex, ASHD Atherosclerotic Heart Disease, COPD Chronic Obstructive Pulmonary Disease, DM Diabetes Mellitus, HT Hypertension, PSA Prostate Specific Antigen

There was no difference among the groups for duration of surgery or estimated blood loss. Anastomosis time was longer in Group 1 compared to Groups 2 and 3. Considering the number of nerve sparing procedures, unilateral neurovascular bundle preservation was done in 19 patients in Group 1, eight patients in Group 2, and 7 patients in Group 3, and the number of patients who had bilateral neurovascular bundle preservation was 19 in Group 1, 13 in Group 2 and 2 in Group 3, without any difference among the study groups for neurovascular bundle preservation rates (p=0.315). Pelvic lymph node dissection rate was 42.2% in Group 1, 32.7% in Group 2, and 52.2% in Group 3, and there was no difference among the groups. A median lobe was detected in 44 (40.4%) patients in Group 1 and in 3 (5.8%) patients in Group 2, however none of the patients in Group 3 had median lobes. There was no difference among the groups for the length of hospital stay, drain removal time or urethral catheter removal time. Final pathology report mean Gleason scores and pathological T stages were similar among the study groups. There was no difference among the groups for extracapsular spread, seminal vesicle invasion or lymph node positivity. Surgical margin positivity was 30.3% in Group 1, 19.2% in Group 2 and 21.7% in Group 3, without any difference (p=0.296). The surgical margin was positivity rate at the bladder neck level was 8.3% in Group 1, 5.8% in Group 2 and 4.3% in Group 3, and there was no difference among the study groups (p=0.774). The complications were graded as Clavien grade 1 in 11 patients and Clavien grade 2 in 16 patients in Group 1; Clavien grade 1 in 4 patients, Clavien grade 2 in 3 patients and Clavien grade 3 in 1 patient in Group 2; and Clavien grade 1 in 1 patient in group 3, and there was no difference among the groups for complication rates (Table 2).

The rate of fully continent patients at the postoperative 1st month was 39.1% in Group 3, 27.5% in Group 1 and 32.7% in Group 2 (p=0.483). There was no significant difference among the groups for the rates of patients with mild, moderate or severe incontinence. The rate of fully continent patients at the postoperative 3rd month was 56.5% in Group 3, 51.9% in Group 2 and 43.1% in Group 1 (p=0.361). At postoperative third month, there was no significant difference among the groups for the rates of patients with mild and severe incontinence, however the rate of moderate incontinence was higher in Group 1 compared to other study groups (p=0.019).

The rate of fully continent patients was 82.6% in Group 3, 73.1% in Group 2 and 61.5% in Group 1 in postoperative 6th month (p=0.079). There was no difference among the groups for mild incontinence rates, however there was a significant difference for moderate incontinence rates (15.6%, 5.8% and 0 for Groups 1, 2 and 3,

respectively) (p=0.034). Severe incontinence was not observed in Groups 2 and 3 in postoperative 6th month.

Table 2: Peri- and postoperative clinical data of the study groups

	Group 1 (n=109) mean (min-max)	Group 2 (n=52) mean (min-max)	Group 3 (n=23) mean (min-max)	p value
Peri-operative parameters;				
Surgery duration (min)	210.8 ± 47.04 (120-420)	201.4 ± 44.4 (90-310)	197.04 ± 32.5 (135-265)	0.39
Anastomosis duration (min)	28.04 ± 9.28 (15-70)	24.6 ± 6.6 (10-45)	22.3 ± 6.3 (10-35)	**0.011***
Estimated blood loss (mL)	266.2 ± 333.04 (25-2000)	188.9 ± 122.7 (10-700)	210.9 ± 162.3 (50-700)	0.93
Nerve bundle preservation;				
-Unilateral	19 (17.4%)	8 (15.4%)	7 (30.4%)	0.32
-Bilateral	19 (17.4%)	13 (25%)	2 (8.7%)	
Lymph node dissection	46 (42.2%)	17 (32.7%)	12 (52.2%)	0.27
Presence of median lobe	44 (40.4%)	3 (5.8%)	0	**0.000***
Postoperative parameters;				
Hospital stay (days)	5.74 ± 3.2 (2-17)	5 ± 2.9 (2-20)	4.96 ± 2.7 (3-14)	0.28
Drain removal time (days)	4.7 ± 3.3 (1-16)	3.8 ± 2.86 (1-19)	4.4 ± 4.96 (1-23)	0.12
Urethral catheter removal time (days)	14.1 ± 2.88 (10-22)	14.7 ± 5.02 (10-43)	14.1 ± 3.8 (10-26)	0.96
Final pathology results;				
Gleason score	6.7 ± 0.75 (6-9)	6.85 ± 0.64 (6-9)	6.78 ± 0.67 (6-9)	0.29
Pathologic T stage; -T2a	26 (23.9%)	9 (17.3%)	6 (26.1%)	
-T2b	3 (2.8%)	0	0	
-T2c	32 (29.4%)	23 (44.2%)	7 (30.4%)	0.46
-T3a	39 (35.8%)	13 (25%)	7 (30.4%)	
-T3b	9 (8.3%)	7 (13.5%)	3 (13%)	
Surgical margin positivity	33 (30.3%)	10 (19.2%)	5 (21.7%)	0.3
Bladder neck surgical margin positivity	9 (8.3%)	3 (5.8%)	1 (4.3%)	0.77
Extracapsular invasion	46 (42.2%)	20 (38.5%)	10 (43.5%)	0.91
Seminal vesical invasion	9 (8.3%)	7 (13.5%)	3 (13%)	0.56
Lymph node positivity	4 (3.7%)	3 (5.8%)	2 (8.7%)	0.71
Complications;				
Clavien-Dindo Grade 1	11 (10.1%)	4 (7.7%)	1 (4.3%)	
Clavien-Dindo Grade 2	16 (14.7%)	3 (5.8%)	0	0.14
Clavien-Dindo Grade 3	0	1 (1.9%)	0	

*statistically significant

Table 3: The incontinence grade rates of the study groups in postoperative 1st, 3rd, 6th and 12th months

		Full continence n(%)	Mild incontinence n(%)	Moderate incontinence n(%)	Severe incontinence n(%)
Postoperative 1st month	**Group 1 (n=109)**	30 (27.5%)	20 (18.4%)	36 (33%)	23 (21.1%)
	Group 2 (n=52)	17 (32.7%)	14 (26.9%)	13 (25%)	8 (15.4%)
	Group 3 (n=23)	9 (39.1%)	6 (26.1%)	6 (26.1%)	2 (8.7%)
	p	0.483	0.405	0.540	0.312
Postoperative 3rd month	**Group 1 (n=109)**	47 (43.1%)	22 (20.2%)	30 (27.5%)	10 (9.2%)
	Group 2 (n=52)	27 (51.9%)	18 (34.6%)	5 (9.7%)	2 (3.8%)
	Group 3 (n=23)	13 (56.5%)	6 (26.2%)	3 (13%)	1 (4.3%)
	p	0.361	0.145	**0.019***	0.467
Postoperative 6th month	**Group 1 (n=109)**	67 (61.5%)	22 (20.2%)	17 (15.5%)	3 (2.8%)
	Group 2 (n=52)	38 (73.1%)	11 (21.1%)	3 (5.8%)	0
	Group 3 (n=23)	19 (82.6%)	4 (17.4%)	0	0
	p	0.079	0.932	**0.034***	0.700
Postoperative 12th month	**Group 1 (n=109)**	79 (72.5%)	22 (20.2%)	6 (5.5%)	2 (1.8%)
	Group 2 (n=52)	42 (80.8%)	8 (15.4%)	2 (3.8%)	0
	Group 3 (n=23)	21 (91.3%)	2 (8.7%)	0	0
	p	0.118	0.344	0.771	1.000

*statistically significant

In the postoperative 12th month, the rate of fully continent patients was 91.3% in Group 3, 80.8% in Group 2 and 72.5% in Group 1 (p=0.118). There were no patients with severe incontinence in Groups 2 and 3, however severe incontinence was detected in 2 (1.8%) patients in Group 1 (Table 3).

Discussion

Incontinence rate following RP has been decreasing thanks to modified surgical techniques, however PPI remains as the most feared complication for men.[13] Continence status is the most important determinant of quality of life in patients who are undergoing RP, and has a more significant effect than erectile function.14

Urinary continence is achieved by the coordination of the urethral suspension mechanism, which consists of the detrusor muscle, internal sphincter, external sphincter and pubourethral ligaments.[15,16] During RP, these structures are partially damaged or completely removed. Therefore, the etiology of postprostatectomy incontinence is multifactorial (de novo detrusor instability, internal sphincter failure, external sphincter failure due to pudendal nerve damage, decreased length of membranous urethra).[17,18]

PPI rates ranging from 4% to 30% have been reported after RARP.7 It has been supposed that this wide difference is mainly due to the lack of standardization regarding the definition of PPI.[19] In a study in which PPI was evaluated with a questionnaire in the 1st year after RARP, the patients were asked "How much urine leakage do you have?", and the responses "Not at all" and "A little" were defined as continence, and "Moderate" and "Much/Very much" were defined as incontinence, and the PPI rate was reported as 14%.[20] In another study, the patients with <20 g urine leakage in the 24-hour pad test were considered continent and the incontinence rate was reported as 6%.4 A prospective, controlled, nonrandomized study compared RARP and RRP, incontinence at the postoperative 12th month was considered as at least one pad changed per 24 h, and the incontinence rate was reported as 21.3% in the RARP arm and 20.2% in the RRP arm.6 As seen in all those studies, a common language has not been developed for the definition of PPI. In our study, 24-hour pad test was used for the standardization of incontinence, and daily urinary incontinence was defined as mild if it was < 100 g,

moderate if it was 100–400 g, and severe if it was >400 g.12 According to the results of our study, in which continence was defined as "no incontinence", the incontinence rate at the postoperative 12th month was 22.8% (regardless of the subgroup analysis), and our results are in line with the literature data.

The relationship between bladder neck preservation during RRP and continence was first investigated by Walsh et al.[21] Over the next 20 years, the effectiveness of sparing bladder neck in open, laparoscopic, and robotic RP procedures has been evaluated, and conflicting results have been published regarding the influence of bladder neck sparing on functional and oncologic outcomes. Preisser et al. compared the patients who had and who did not have bladder neck preservation during RARP, reported a lower incontinence rate in the ones who had bladder neck preservation only in the 1st week, after urinary catheter removal (60.0% vs. 54.5%), and no difference between the groups at the 3rd and 12th months (80.1% vs. 78.3% at third month and 85.3% vs. 89.6% at first year for bladder neck sparing and bladder neck reconstruction groups, respectively).[22] Freire et al. evaluated the effectiveness of bladder neck sparing in their RARP series, reported that the continence rates 65.6% versus 26.5% ($p<0.001$) at the postoperative 4th month in favor of bladder neck sparing, and the groups were similar in terms of continence at 12th and 24th months.[23] To determine the effective periprostatic structures in the early improvement of urinary continence following RP, Sood et al. evaluated the individual effects of preservation of nerves, bladder neck and Retzius space on early continence by comparing different RARP methods. The authors stated that the methods that preserved the bladder neck (posterior and hybrid method) had the highest continence rates in the 1st week and 1st month after RARP. They concluded that bladder neck preservation was the only significant predictor of early recovery of continence.[24] In our study, although there was no difference among the groups for incontinence rates, it was observed that bladder neck preservation reduced the severity of incontinence.

Li et al. showed that PPI improved gradually within one year after RARP and remained stable after the first year.[25] Ficarra et al. reviewed urinary continence improvement after RARP in a meta-analysis, and reported that PPI gradually decreased in the 1st postoperative year following RARP (PPI rates at 3, 6, and 12 months were 35%, 12%, and 9%, respectively).[7] In our study, incontinence rates decreased gradually in all groups until the postoperative 1st year and reached their lowest levels in the 1st year visits.

The major concern for sparing bladder neck is leaving a positive surgical margin at the level of bladder neck. In a series of 1512 RARP patients, the authors investigated the influence of sparing bladder neck on continence and biochemical recurrence, and found surgical margin positivity as 12.7% in the ones who did not have bladder neck preservation and 9.9% in the ones who had bladder neck preservation ($p=0.3$).22 Dal Moro et al. compared 88 RARP patients who had extreme bladder neck preservation with 88 RARP patients with similar characteristics who did not have bladder neck preservation, and stated that the surgical margin positivity at the bladder neck level was similar in two groups (5.7% in the extreme bladder neck spared group, 6.8% in the bladder neck unspared group). The authors concluded that extreme bladder neck preservation was oncologically safe.[11] In our study, surgical margin positivity rates at the bladder neck level were found as 8.3%, 5.8% and 4.3% in Groups 1, 2 and 3, respectively, and no difference was determined among the study groups in terms of surgical margin positivity.

Retrospective design and limited number of patients included are the major limitations of our study. Prospective randomized studies on a larger patient cohort are needed.

Conclusions

The results of this study showed that the methods that preserve the bladder neck during RARP do not have a significant effects on the continence rates, however they reduce the severity of incontinence. At the same time, bladder neck sparing procedures have been shown to be oncologically safe.

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RESEARCH ARTICLE

A Retrospective Analysis of Cases of Non-Immune Hydrops Fetalis in A Tertiary Center

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Abstract

Introduction: Non-immune hydrops fetalis (NIHF) can occur at different gestational ages and with different etiologies. The aim of this study was to investigate the association of gestational age at diagnosis and a novel clinical scoring system with survival in NIHF cases **Methods:** This retrospective study was conducted between January 2020 and January 2023 in the perinatology clinic of a tertiary care center. Maternal characteristics, causes of NIHF, and survival rate were analyzed. The hydrops score was calculated and compared for those less than and greater than 20 weeks. **Results:** Of 41 NIHF, etiology was determined in 76% (87% <20 weeks vs. 70% ≥20 weeks), including cardiovascular malformations (27%), cystic hygromas (17%), and chromosomal defects (12%). Cystic hygromas were more common before 20 weeks. Cardiac malformations were the most common cause after 20 weeks. There was a negative correlation between live birth and hydrops score. The overall survival was 7.3%. The most favorable overall survival is in NIHF cases associated with fetal arrhythmias and placental pathology for the second and third trimesters, respectively. **Conclusion:** Earlier gestational age at diagnosis and higher hydrops score are associated with lower survival rates in NIHF cases. Determining the cause, accompanying structural abnormalities, and the week NIHF is diagnosed will help predict prognosis and apply treatments earlier to improve care for these fetuses and newborns

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Introduction

Non-immune hydrops fetalis (NIHF) is a complex condition defined as excessive fluid accumulation in two or more fetal compartments, such as skin, pleura, pericardium or peritoneum, and placenta.[1] NIHF occurs in 1 in 2000-3500 live births. A heterogeneous group of conditions, including hematologic, cardiovascular, chromosomal, infectious, syndromic, thoracic, and idiopathic, can cause NIHF.

The Maternal-Fetal Medicine Society has developed recommendations for evaluating the hydropic fetus, including maternal blood tests, comprehensive ultrasonography of the fetus and placenta, fetal echocardiography, middle cerebral artery doppler studies, and a fetal karyotype.[2] Cases of aneuploidy can be diagnosed by karyotype or chromosomal microarray analysis; however, in some cases, the etiology remains unclear even after standard testing.[3] If necessary, more specialized tests should be recommended. Despite extensive investigation, the cause of 15-25% of NIHF cases is unclear—the causes of hydrops influence overall morbidity and mortality.[4] Identifying NIHF-related causes is critical for prenatal counseling and managing subsequent pregnancies.

This study aims to determine the etiology and outcome of NIHF concerning gestational age at diagnosis in the prenatal period.

Material and Methods

This retrospective study was conducted between January 2020 and January 2023 in the perinatology clinic of a tertiary care center. Medical records of all cases diagnosed with NIHF were analyzed. Consent for data and image recording was obtained from all patients, the Ethics Committee approved the study, and the Declaration of Helsinki was followed (E2-23-3837).

Fetal hydrops was defined as cystic hygroma or excessive fluid accumulation in more than two fetal body cavities. Cases with hydrops due to isoimmunization were excluded from the study, and patients diagnosed with NIHF at any week of gestation were included. Karyotype analysis was performed in patients who accepted chorionic villus sampling, amniocentesis, or cordocentesis. Patients were screened prenatally for anatomic malformations that could cause hydrops, antibodies to red blood cells, peak systolic middle cerebral artery velocity, and maternal infections (cytomegalovirus, toxoplasmosis, syphilis, parvovirus B19). Each patient underwent a comprehensive sonographic examination according to gestational age. Fetuses with increased nuchal translucency (NT) and cystic hygromas were included in the study between 11-13+6 weeks of gestation. The compartments of fluid accumulation, concomitant fetal anomalies, and fetal anemia findings were assessed. Abnormal NT was defined as > 95% percentile for crown-rump length. Maternal characteristics, serologic results, sonographic findings, pregnancy outcomes, survival rates, stillbirths, or neonatal deaths were recorded. The possible etiologic causes of NIHF were classified, and the causes were identified before and after 20 weeks of gestation. The hydrops fetalis score was calculated using information obtained by fetal ultrasound and doppler examination, and its association with survival was analyzed between the live birth group and the group of intrauterine exitus or termination of pregnancy (TOP). Five parameters were evaluated: (1) Maternal age, <35, ≥35 (2) Gestational age at diagnosis <20, ≥20 weeks (3) Fetal hydrops components, pleural effusion, abdominal assit, cystic hygroma (4) Doppler flow velocimetry of the ductus venosus (5) Cardiac function: Tricuspid regurgitation, mitral regurgitation, arrhythmia, major cardiac anomaly (Table 1).

SPSS version 22.0 software (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. Descriptive data were expressed as frequencies and percentages. Pearson's chi-square and Fisher's exact tests were used to analyse categorical data. The "independent sample t" test was used to compare the measurements of two groups when normally distributed. The "Pearson" correlation coefficient was used to examine the relationship between groups. A p-value of less than 0.05 was considered statistically significant.

Table 1. Parameters used in hydrops scoring

Maternal age (years)	**Gestational age of diagnosis (weeks)**	**Hydrops compartment**	**Ductus venosus doppler**	**Cardiac function**
<35: 0 ≥35: 1	<20: 1 ≥20: 0	Cystic hygroma: 1 Pleural effusion: 1 Abdominal ascites: 1 Skin edema: 0	Normal: 0 Reverse: 1	Tricuspid regurgitation: 1 Mitral regurgitation: 0 Arrhythmia:1 Major cardiac anomaly: 1

Results

Forty-one pregnancies with NIHF were analyzed. The mean maternal age was 31.5 years (24-44 years), and the mean gestational age at the initial

diagnosis was 22 weeks (11-34 gestational weeks). The etiology of NIHF could be determined in 76% (n=31) of cases, while it remained undetermined in the remaining 24% (n=10) cases. The most common condition associated with NIHF was cardiovascular malformations (11 cases, 27%), followed by cystic hygromas (7 cases, 17%) and chromosomal defects (5 cases, 12%). Subgroup analysis revealed that gestational age was less than 20 weeks in 17 cases and between 20 and 40 weeks in 24 cases. Chromosomal abnormalities and cystic hygromas occurred more frequently before 20 weeks gestation, whereas cardiac malformations were the most common cause after 20 weeks. The rate of cystic hygromas was statistically significantly higher before 20 weeks of gestation than after 20 weeks (Table 2). Hypoplastic left heart syndrome (HLHS) (27%) was the most common cardiovascular malformation, followed by pulmonary atresia with ventricular septal defect (18%) and pulmonary hypoplasia (18%) (Table 3). Chromosomal abnormalities detected at NIHF included trisomy 21, trisomy 18, trisomy 13, Turner syndrome, and triploidy (Table 4).

Table 2. Analysis of Non-Immune Hydrops Fetalis Based on Gestational Age

Parameters	<20 week (n=15)	20-40 week (n=26)	p-value
Congenital Cardiac defects	2	9	0.04
Chromosomal abnormality	4	1	0.06
Cystic hygroma	6	1	0.00
Skeletal dysplasia	0	2	0.22
Cardiac tumor	0	1	0.39
Cardiac arrhythmia	0	3	0.66
Placental chorioangioma	0	1	0.39
Partial molar pregnancy	1	0	0.18
Idiopathic	2	8	0.17
Live birth	0 (0%)	14 (53.8%)	0.00

p-value <0.05 was considered statistically significant.

Table 3. Cardiovascular Causes of Non-Immune Hydrops Fetalis

Cardiac anomaly	Number of cases, n	Percentage
Hypoplastic left heart syndrome	3	27%
Pulmonary hypoplasia	2	18%
Pulmonary atresia with ventricular septal defect	2	18%
Tetralogy of fallot	1	9%
Critical aortic stenosis	1	9%
Hypoplastic right ventricle	1	9%
Tricuspid atresia and pulmonary atresia	1	9%

Table 4. Chromosomal abnormalities

	Number of cases, n
Trisomy 21	1
Turner syndrome	1
Triploidy	1
Trisomy 18	1
Trisomy 13	1

Fourteen infants were born alive (34%), and three infants were discharged alive from the hospital. The overall survival rate was 7.3%. The defined etiology of hydrops in the surviving fetuses was placental chorioangioma, fetal supraventricular tachycardia, and idiopathic cause. The mean hydrops score of the group with intrauterine exitus or TOP was significantly higher than the live birth group (4.4±1.0 vs. 3.6±1.2 p=0.04). Correlation analysis showed a weak negative correlation between live birth and hydrops score (r=0.30, p=0.06). In the group that died after birth, median survival ranged from 60 minutes to 51 days. Live-born cases are shown in Table 5.

Table 5. Live Born Cases with Non-Immune Hydrops Fetalis

	Gestational age at diagnosis of NIHF (weeks)	Gestational age at birth (weeks)	Weight (g)	Gender	Survival time	Etiology
1	22	30	2450	M	31 day	Fetal arrhythmia (atrioventricular block)
2	26	32	2710	M	3 hour	Skeletal dysplasia
3	23	27	1550	M	21 day	Fetal arrhythmia (supraventricular tachycardia)
4	26	29	1820	M	1 hour	Idiopathic
5	28	31	1770	F	Healthy	Placental chorangioma
6	28/4	33/4	2100	F	51 day	Cardiac anomaly (Tetrology of fallot)
7	34/4	37	2560	F	Healthy	Idiopathic
8	25	25/5	1540	M	9 hour	Cardiac anomaly (Aortic stenosis)
9	21/5	29/2	1500	F	5 hour	Cardiac anomaly (Hypoplastic right heart syndrome)
10	32/4	38	3060	F	3 hour	Skelatal dysplasia
11	24	30	1500	F	1 hour	Cardiac anomaly (Pulmonary and tricuspid atresia)
12	22	35	2260	F	Healthy	Fetal arrhythmia (Supraventricular tachycardia)
13	31	32	2850	M	1 hour	Cardiac anomaly (Pulmonary hypoplasia)
14	30	34	2250	M	2 hour	Idiopathic

F, female; M, male.

Discussion

In this study, the causes of prenatally diagnosed cases of NIHF were investigated and classified according to gestational age. Our results suggest that the leading cause of NIHF after 20 weeks of gestation

is cardiovascular abnormalities, with HLHS being the most common cause. The etiology can be identified in up to 80% of prenatally diagnosed NIHF cases, with the most favorable overall survival in NIHF associated with fetal arrhythmias and placental chorioangiomas. NIHF is caused by several etiologic variables that may be maternal, fetal, or placental. Impaired vascular permeability, lymphatic drainage due to changes in osmotic pressure, and impaired venous pressure balance are the physiologic factors that cause NIHF.5 The etiology can be determined in 60-85% of cases prenatally or postnatally.[6] The remaining cases are considered idiopathic (i.e., no prenatal or postnatal anatomic malformations were detected, no maternal antibodies to red blood cells, normal peak systolic velocity in a middle cerebral artery, no known monogenetic disorders, fetal tumors, and negative screening for maternal infections (e.g., cytomegalovirus, toxoplasmosis, syphilis, parvovirus B19), euploid fetal karyotype.[6],[7] Cardiac etiologies of hydrops fetalis account for 10-20% of diagnosed NIHF in the prenatal period, including structural cardiac abnormalities, arrhythmias, cardiac tumors, and cardiomyopathy.[8] In our study, cardiac causes of NIHF accounted for 39% of all etiologic causes. Of these, 75% (n=11) were cardiac malformations, 19% (n=3) were cardiac arrhythmias, and 6% (n=1) were NIHF due to cardiac tumors. Cardiac malformations can be simple or complex.[9],[10] Our study found that the most common cardiac abnormality causing hydrops was HLHS. The two leading causes of hydrops fetalis are hemodynamic changes and conduction abnormalities associated with congenital structural heart defects. These congenital structural heart anomalies have been associated with significant left heart problems, such as HLHS, often associated with a narrowed foramen ovale, massive atrioventricular defect, and severe aortic stenosis. Because HLHS with normal venous Doppler measurements and normal cardiovascular function has a low risk of fetal death in utero.[11]-[13] According to some authors, the most common cause of NIHF is a right heart defect causing increased pressure and venous volume overload.[14] Another explanation for NIHF in HLHS is outflow obstruction due to severe aortic stenosis, which can lead to myocardial dysfunction of the left ventricle. The excess volume then causes dysfunction of the right ventricle, leading to intrauterine heart failure, which manifests as hydrops fetalis.[15],[16] A case of HLHS with concomitant hydrops has been described in the literature as tricuspid stenosis characterized by increased central venous pressure and abnormal venous Doppler measurement leading to fetal hydrops.[17] This fetus has significant atrial systolic flow reversals in the ductus venosus and pulsatility in the umbilical vein. Such reversals in the fetus indicate high central venous pressures.[18],[19] In our study, two cases of HLHS were associated with severe mitral and aortic hypoplasia, and one HLHS case was associated with Turner syndrome, which has an abnormal lymphatic system circulation. One of the most common causes of NIHF is cardiac arrhythmias. Fetal tachyarrhythmias such as supraventricular tachycardia (SVT) result in increased atrial pressure and decreased cardiac output, leading to heart failure. Based on pathogenesis, arrhythmias are the most treatable cardiac causes of hydrops fetalis.[20] Severe bradyarrhythmias accompanied by SVT and complete heart block are common and serious fetal arrhythmias. Hydrops fetalis may be caused by a congenital atrioventricular heart block, which has been shown to respond effectively to transplacental treatment or direct fetal therapy.[21] Our study found cardiac arrhythmias in 3 fetal hydrops, including SVT in 2 fetuses, and congenital complete AV block in 1 fetus. Despite intrauterine salbutamol treatment in a fetus with complete AV block, no improvement was noted, and birth occurred in the 30th week. A pacemaker was implanted in the newborn after birth, and died on postnatal day 31 due to cardiac arrest. Intrauterine digoxin treatment was initiated in two fetuses diagnosed with SVT. In both cases, SVT improved one day after treatment. One of the two fetuses was delivered at 27 weeks gestation because of fetal distress, and at the third week after birth, the fetus died because of systolic dysfunction. Hydrops and SVT attacks of the other fetus improved with antiarrhythmic treatment in the postnatal period, and the newborn was discharged with medication. Cardiac tumors also can cause NIHF by causing cardiac arrhythmias and obstruction of vascular outflow.[22] In a retrospective analysis, 84 cases of fetal tumors were studied. Cardiac tumors accounted for 23.8%, causing arrhythmias in 42% of cases.[23] In our study, patient with fetal cardiac tumor preferred to terminate pregnancy in an external center at 19 weeks of gestation. NIHF occurs in approximately 5-6% of cases with lymphatic dysplasia 2. Increased nuchal translucency, cystic hygromas, and chylothorax are common in Turner syndrome, especially in the first trimester, but also occur in other genetic syndromes such as mul-

tiple pterygium syndrome and RASopathies such as Noonan syndrome.[24] In our study, 17% of cases were found to have cystic hygroma. These cases were mostly observed in the first trimester, which was statistically significant.[25] Genetic examinations such as karyotyping and microarray analysis are the recommended first-line tests for NIHF cases. They can detect 7-17% of NIHF cases due to chromosomal abnormalities and copy number variants.[3],[25] However, microarray analysis cannot be routinely performed in our country due to its high cost. Trisomy 21, trisomy 18, trisomy 13, triploidy, and Turner syndrome were detected in a small group of patients who requested karyotype analysis. Placental pathologies should also be considered as potential etiologies of NIHF. Chorioangioma, umbilical cord angiomyxoma, and umbilical artery aneurysm are rare diseases of the placenta and umbilical cord associated with NIHF.2 It is unclear in which trimester NIHF due to placental pathology is more frequent, but the extent of pathology influences the week of hydrops formation. Large placental chorangiomas (> 5 cm) are likely to result in rapid NIHF due to high-output heart failure.[2] In our study, NIHF cases occurred in the first trimester due to partial mole and in the second trimester due to chorangioma. One of the surviving fetuses in our study was hydrops due to placental chorioangioma. The blood supply of the chorioangioma was destroyed by diode laser coagulation at 28 weeks of gestation. After the procedure, fetal hydrops improved, and delivery occurred at 32 weeks of gestation. A healthy infant is in follow-up. Once the NIHF etiology is determined, hydrops scoring can help interpret the prognosis. The hydrops scoring parameters in our study were partially similar to the few studies in the literature. We found a significantly lower hydrops score in the live birth group and a negative correlation between hydrops score and fetal outcome. In the literature, the proportion of idiopathic etiology in NIHF cases varies, with about one-third classified as idiopathic. Prenatal examinations contributed to the increase in etiology detection rates. Definitive diagnoses are more common in early gestation. A previous study found that 83.3% of 19 cases with NIHF in the first trimester were associated with structural abnormalities and 47.3% with chromosomal abnormalities.[26] In our study, 13% of NIHF cases were idiopathic before 20 weeks, whereas this rate was 30% after 20 weeks. In some cases, an autopsy may help determine the underlying cause. A significant limitation of our study is that most patients did not undergo genetic testing or fetal/neonatal autopsy, so these cases were described as idiopathic. One of the advantages of our study is that we have investigated and described in detail the etiology of NIHF in a tertiary center with a large number of cases. Although several etiologic causes have been identified, the survival rate in NIHF is very low because of limited treatment options. The overall survival rate was 7.3%. Median survival in the group that died after birth ranged from 60 minutes to 51 days.

Conclusion

NIHF is caused by a heterogeneous group of underlying diseases. Cardiovascular abnormalities are the main cause of NIHF after the mid-trimester. The prognosis of NIHF cases diagnosed in the first trimester is very poor, and the survival rate of NIHF due to fetal arrhythmias and placental abnormalities in advanced weeks of gestation is relatively high. Determining the cause, accompanying structural abnormalities and the week NIHF is diagnosed will help predict prognosis and apply earlier treatments to improve care for these fetuses and newborns.

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Conflict of interest
The authors report there are no competing interests to declare

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RESEARCH ARTICLE

Evaluation of platelet and inflammatory indices in isolated gestational proteinuria in term pregnancies

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Abstract

Introduction: Isolated gestational proteinuria (IGP) is new onset gestational proteinuria after 20 weeks of gestation in which the pregnancy is to be completed with normal maternal blood pressure and no signs of preeclampsia with no history of hypertension, diabetes, malignancy, autoimmune or kidney disease. IGP can be the first symptom of preeclampsia, however there is no consensus on whether IGP is a mild form of preeclampsia, in which immunologic factors and inflammation take role in pathogenesis. Platelet and inflammatory indices are changed under inflammation as under systemic inflammation neutrophilia, lymphopenia and thrombocytosis and platelet activation occur. Platelet indices are mean platelet volume (MPV) and platelet volume distribution width (PDW). Inflammatory indices include neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio(PLR). This study compared the platelet and inflammatory indices between IGP and healthy pregnancies. **Methods:** Thirty-two IGP and 60 healthy term pregnancies were recruited. Proteinuria was detected in 24-hours urine sample if proteinuria exceeded 300 mg/day. Platelet and inflammatory indices were obtained and calculated from complete blood count test. The groups were compared with respect to participant characteristics, MPV, PDW, NLR and PLR. $p<0.05$ was considered statistically significant. **Results:** : There was no significant difference among the two groups in terms of participant characteristics, pregnancy outcomes. The platelet and inflammatory indices were not significantly different between the groups. **Conclusion:** Mean platelet volume, PDW, NLR and PLR were not significantly different between healthy and IGP pregnancies. The pathophysiology of IGP is still controversial in the literature, but this study showed that inflammatory status was not different in IGP pregnancies than healthy pregnancies.

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Introduction

Gestational proteinuria is diagnosed when the amount of protein excretion in urine exceeds 300 mg in 24 hours during pregnancy.[1] Gestational proteinuria may indicate presence of preeclampsia or renal pathologies.[2] Approximately 30% of gestational proteinuria may be the first sign of preeclampsia.[3,4] Preeclampsia, presents as new onset hypertension with proteinuria or end-organ dysfunction after 20 weeks of gestation with no history of hypertensive disease.[5] There are several pathogenetic pathways under preeclampsia such as immunologic factors, genetic factors and inflammation. In the placental bed natural killer cells are increased and regulatory T cells are decreased.[6] With additional placental hypoxia, trophoblastic necrosis occurs and fetal DNA is released to the maternal circulation. These factors trigger maternal systemic inflammation.[7]

Isolated gestational proteinuria (IGP) is different from preeclampsia and presents as new onset gestational proteinuria after 20 weeks of gestation in which the pregnancy is to be completed with normal maternal blood pressure and no signs of preeclampsia (low platelet count, elevated liver enzymes, blurred vision etc.). To diagnose IGP there should be no history of hypertension, diabetes, malignancy, autoimmune or kidney diseases.[2]

Inflammatory and platelet indices are obtained from complete blood count tests which are widely performed during pregnancy follow-ups. Platelet indices include mean platelet volume (MPV) and platelet volume distribution width (PDW). These indices reflect platelet activation.[8] Inflammatory indices include neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. The two indices change under inflammation as under systemic inflammation neutrophilia, lymphopenia and thrombocytosis and platelet activation occur. By using aforementioned indices inflammatory status can be revealed.

This study was designed to investigate whether IGP is also associated with inflammation unlike healthy pregnancies. To achieve this, the platelet and inflammatory indices were compared between healthy and IGP pregnancies.

Material and Methods

This study was a retrospective cohort study. The study protocol was appropriate to the Declaration of Helsinki, and ethical approval was obtained from the Ethical Committee of Kocaeli Derince Education and Research Hospital (Approval Date/Number: 08.12.2022/136). A total of 92 pregnant women age between 18 and 45, with a gestational age at least 37 weeks were recruited. This study took place in the Obstetrics and Gynecology Clinics of Kocaeli Derince Education and Research Hospital, between June 2021 and December 2022. The participants of this study were singleton pregnant women without any known comorbidities who were antenatally followed and collected 24-hours urine sample after positive proteinuria (+1 and +2) in spot urine test. The study group involved 32 pregnant women who were diagnosed only with IGP. Isolated gestational proteinuria was defined as new onset gestational proteinuria after 20 weeks of gestation in which the pregnancy is to be completed with normal maternal blood pressure and no signs and symptoms of preeclampsia during pregnancy. These pregnant women had no history of hypertension, diabetes, malignancy, autoimmune or kidney disease.[2] Preeclampsia was diagnosed with respect to ACOG criteria.[9] All participants were evaluated by urine culture. Pregnancies with urinary tract infection, multiple pregnancies, preeclamptic pregnancies, pregnant women with previous history of proteinuria or kidney disease, hypertension, pregestational and gestational diabetes, autoimmune disease and current low glomerular filtration rate, positive urinary sediment, positive nitrite in spot urine test were excluded. The control group consisted of healthy pregnancies without any comorbidities during the same period of participant recruitment. The weight and height of the pregnant women were recorded for body mass index (BMI) calculation. BMI was calculated as weight (kg)/(height ^{2}(m^2). All of the participants were followed up weekly till 6 weeks after the delivery. In the postpartum period, patients were asked to measure arterial hypertension twice a day each week, informed and evaluated for preeclampsia signs and symptoms to exclude postpartum preeclampsia. The patients developing preeclampsia were also excluded from this study.

Maternal venous blood samples obtained for complete blood count analysis, kidney function tests, liver function tests and c-reactive peptide. Blood samples were centrifuged at 3000 RPM for 10 minutes, and serum samples were analyzed for hemoglobin, white blood cell count, platelet count, platelet distribution width, mean platelet volume, neutrophil count, lymphocyte count,

alanine transaminase, aspartate transaminase, creatinine, uric acid, albumin and C-reactive protein.

The statistical analysis of the study was performed using SPSS 20.0 (IBM, USA). Numerical data determined to be normally distributed based on the results of Shapiro-Wilk test are given as mean ± standard deviation (SD) values, while non-normally distributed variables are given as median (25th-75th quartiles, IQR) values. In comparing numerical variables between two groups, the Student's T-test (for those showing a normal distribution) and the Mann Whitney-U test (for those not showing a normal distribution) were used. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher exact tests. Significance was accepted at $P < 0.05$ (*) for all statistical analyses.

Results

A total of 92 pregnancies were involved in this study. There was no significant difference among the two groups in terms of maternal age, gestational age, BMI, number of gravida, parity, and abortus (Table 1).

Table 1: Maternal characteristics and pregnancy outcomes of the participants.

Maternal Characteristics	Pregnancies with isolated proteinuria n=32	Pregnancies without isolated proteinuria n=60	p
Age, years	26 (23-31)	30 (24-36)	0.084
Gravida	3 (1-4)	3 (1-4)	0.488
Parity	1 (0-2)	1 (0-2)	0.748
Abortus	0 (0-1)	0 (0-0)	0.178
BMI, kg/m^2	23.9 (19.7-27.6)	24.3 (19.5-26.3)	0.407
Pregnancy Outcomes			
Birth weight, g	3000 (2420-3300)	2780 (2550-3245)	0.407
Gestational age at delivery, weeks	38.3 (37.3-39.0)	38.0 (37.0-39.5)	0.935

Data are mean ± standard deviation or median (IQR). Abbreviations: BMI: body mass index.

Pregnancy outcomes did not show a significant difference in birth weight, gestational age at delivery, neonatal intense care unit admission (p=0.463), amniotic fluid index at term (p=0.744), delivery mode (p=0.295), number of fetal growth retardation or appropriate for gestational age fetuses (p=0,473 and p=0,115 respectively).

Table 2: Laboratory results and indices of the participants.

Laboratory Parameters	Pregnancies with Isolated proteinuria n=32	Pregnancies without Isolated proteinuria n=60	p
Hemoglobin, g/dL	11.2 ± 1.3	11.8 ± 1.14	**0.049***
WBC, x10^{-3}/microL	9.752 ± 2.08	10.061 ± 2.44	0.589
PDW, %	17.3 ± 2.79	17.6 ± 2.50	0.612
MPV, fL	9.12 ± 0.88	9.22 ± 0.80	0.595
Neutrophil count, x10^{-3}/microL	6.99 ± 1.8	7.16 ± 2.06	0.726
Lymphocyte count, x10^{-3}/microL	1.93 ± 0.49	1.90 ± 0.52	0.772
Proteinuria, mg/24 hours	632 (407-837)	277 (157-281)	0.097
Platelet count, x10^{-3}/microL	264 (218-313)	226 (201-271)	0.119
MPVxPLT	2.3 (1.96-2.72)	2.1 (1.8-2.44)	0.222
PLR	131 (103-207)	133 (108-158)	0.585
NLR	3.6 (3.0-4.3)	3.7 (3.1-4.5)	0.867
PLT/N	37.0 (32.0-45.4)	35.0 (26.8-42.5))	0.220
ALT, U/L	9 (8-12)	11 (8-14)	0.056
AST, U/L	17 (13-19)	17 (14-22)	0.408
Creatinine, mg/dL	0.59 (0.55-0.65)	0.58 (0.54-0.66)	0.613
Uric acid, mg/dL	4.4 (3.9-5.6)	3.9 (3.3-4.6)	**0.042***
Albumin, g/dL	3.3 (3.1-3.6)	3.3 (3.0-3.6)	0.661
CRP, mg/L	2.0 (2.0-5.0)	2.0 (2.0-3.8)	0.853

Data are mean ± standard deviation or median (IQR). *p<0.05 indicates statistical significance. Abbreviations: WBC: White blood cell, PDW: platelet distribution width, MPV: mean platelet volume, PLT: platelet, PLR: platelet leukocyte ratio (platelet count/leukocyte count), NLR: neutrophil leukocyte ratio (neutrophil count/leukocyte count), N: neutrophil, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, IQR: interquartile range, SD:standard deviation

There was no significant difference between laboratory parameters of two groups except hemoglobin and uric acid levels. Platelet indices were not significantly different between the groups.

Discussion

This study was designed to compare inflammatory status by using platelet and inflammatory indices between healthy pregnancies and pregnancies with isolated gestational proteinuria. To

our knowledge, this was the first study designed to evaluate platelet and inflammatory indices in IGP.

The study and the control groups did not differ by means of gestational and maternal age. The blood draw period was limited to term pregnancy in order to exclude preeclamptic pregnancies. Platelet indices which are mean platelet volume (MPV) and platelet volume distribution width (PDW) and inflammatory indices which include neutrophil-lymphocyte ratio; and platelet-lymphocyte ratio were not significantly different between the groups. By this result, we showed that inflammatory status was not altered in isolated gestational proteinuria with respect to healthy pregnancies.

Previous studies by Thalor et al. and Bawore et al. showed that the platelet indices, especially the MPV and PDW were significantly increased in preeclampsia.[10,11] NLR was found to be significantly higher in preeclampsia whereas PLR was lower in preeclamptic pregnancies.[12] Systemic inflammatory response takes place in the pathophysiology of preeclampsia and inflammatory and platelet indeces were altered.[2] Maynard et al. showed that increased placental soluble fms-like tyrosine kinase 1 decreased VEGF and PIGF which created endothelial dysfunction, oxidative stress and inflammation leading to proteinuria and preeclampsia.[13] In the prospective study of Holston et al. these angiogenic factors were studied in IGP. They have concluded that IGP could be defined as mild version of preeclampsia.[14] They showed IGP was associated with lower levels of PIGF and transiently elevated soluble fms-like tyrosine kinase and soluble endoglin concentrations before the onset of proteinuria.[14] Besides, it is known that 30% of isolated gestational proteinuria progresses to preeclampsia.[3,4] However, we think that isolated gestational proteinuria pregnancies who will have future preeclampsia and will not have, are not the same and might have pathophysiological differences underneath. Because in this study, IGP pregnant women without preeclampsia progression, did not have altered inflammatory and platelet indices from healthy pregnancies. In addition to this, Kattah et al. also hypothesized that IGP should not be taken into account as mild preeclampsia because they found no association of nulliparity with IGP but it is known that preeclampsia is associated with nulliparity.[14] Another limitation of the study of Holston was, the follow up of pregnant women ended after only 24 hours after delivery. It was shown that postpartum preeclampsia could occur in pregnancies with IGP and pregnant women should be followed at least 48 hours to 6 weeks after pregnancy for preeclampsia.[15,16]

Hemoglobin and uric acid levels between the groups were statistically significant but these had no clinical significance. Mean hemoglobin and median uric acid levels of both groups were in normal ranges.

The limitations of this study were, the two clinical situations, transient or orthostatic proteinuria could not be ruled out as 24-hour urine sample was evaluated only once before delivery. Secondly, this study was performed with a small sample size and was a single center study. Proteinuria status of women with IGP after delivery and preeclamptic pregnancies were not in the scope of this study. A future study might be performed to compare inflammatory and platelet indices of preeclamptic, healthy and IGP pregnancies together and follow proteinuria status after the delivery.

Conclusion

Mean platelet volume, platelet volume distribution width, neutrophil-lymphocyte ratio; and platelet-lymphocyte ratio were not significantly different between healthy and IGP pregnancies. The pathophysiology of IGP is still controversial in the literature, but this study showed that inflammatory status was not different in IGP pregnancies than healthy pregnancies.

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RESEARCH ARTICLE

The Effect of Ticagrelor on Survival of Skin Flap in Rat Model

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Abstract

Introduction: Necrosis due to ischemia at the distal end of a flap is an important problem encountered during flap operations. Several procedures and drugs including delayed procedures, leeches, and anticoagulants, can be used to maintain flap viability. **Methods:** Sixteen rats were randomly divided into two groups of eight: the ticagrelor and the control groups. Rats in the ticagrelor group were administered ticagrelor diluted with 0.3 mL of saline at a dose of 10 mg/kg twice a day for 7 days, starting at 2 h preoperatively and 10 h postoperatively, by oral gavage. Similar stress in the control group was induced orally with saline solution at the same time. The results were statistically analyzed for both clinical and histopathological evaluations. **Results:** During the clinical examination, the area of necrosis and the entire flap area were measured using transparent acetate paper (grid method). In the histopathological examination, tissue samples were taken from the transition zone between necrotic tissue and intact tissue in the flaps of rats sacrificed on the 7th day. There were significant differences in clinical evaluation. ($p<0,05$) The mean and SD of necrosis were 15,65±1,84 cm^2 in the control group and 8,59±3,75 cm^2 in ticagrelor group. There were no significant differences ($p>0,05$) in the histopathological examinations; however, compared with the control group, fewer inflammatory cells and necrosis were observed in the ticagrelor group. **Conclusion:** We found a statistically significant difference in clinical outcomes with the use of ticagrelor. However, no significant differences were found in the histopathological observations. Our results suggest that ticagrelor is effective on survival of skin flaps of rats in clinical evaluation.

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Introduction

Flaps are used to repair tissue defects during plastic and reconstructive surgeries. When a flap is harvested, its circulation is disrupted. Sympathetic innervation is acutely lost, and neurotransmitters that cause vasoconstriction are released spontaneously.[1] One of the important problems encountered in flap operations is necrosis due to ischemia at the distal end of the flap. In the literature, several procedures and drugs have been shown to maintain flap viability, such as delayed procedures, leeches, and anticoagulants.[2-6] Ticagrelor is an oral P2Y12 inhibitor that selectively and reversibly binds adenozin diphosphate (ADP) receptor antagonists on the ADP receptor. It has vasodilator, antiplatelet, and antithrombotic effects.[7,8] However, the effect of ticagrelor on random-pattern skin flaps was not investigated. Here, we designed to examine whether these features of ticagrelor have positive effects on the viability of random-pattern skin flaps according to previous studies.[9-12]

Material and Methods

All animal experiments were approved by the Institutional Animal Care and Use Committee (Decision Number: 2016-9-101). Sixteen Wistar albino rats, weighing 200–300 g, were used. The rats were randomly divided into two groups of eight: ticagrelor and control groups. The animals in the ticagrelor group were administered ticagrelor (Brilinta, AstraZeneca, UK) diluted in 0.3 ml of saline at a dose of 10 mg/kg twice a day for 7 days, starting at 2 h preoperatively and 10 h postoperatively, by oral gavage. To induce similar stress in the animals in the first group, the same volume of saline was administered orally at the same time.

The subjects were anesthetized by administering intramuscular ketamine hydrochloride (Ketalar, Pfizer) and xylazine hydrochloride (Rompun, Bayer). The surgical field was prepared under anesthesia. The rats were placed in a prone position. A 3 × 10 cm caudal-based McFarlane flap[13] was planned and elevated from the dorsum of each rat. The flap was then adapted to its location using a running technique with a 3/0 polyglactin (Vicryl, Ethicon) suture not to occur a wound dehiscence.

The results were examined by clinical evaluation, including planimetric measurement and Image J program (USA), and histopathologic evaluation. Statistical analyses were performed using SPSS software version 20.0 (IBM, USA). While performing the data analysis, the Independent 2-group t-test (Student's t-test) was used for the comparison of the two groups, and the Mann Whitney-U test was used if the prerequisites were met. Categorical contents were analyzed with Fisher's Exact Test and Chi-Square test. The rats were sacrificed on the 7th day and were photographed at a distance of 40 cm. Images were transferred to the Image J program. The reason which was chosen the 7th day that new anastomoses formed between a flap and a recipient site become active from the 5th-7th day. From the 7th day, there is no increase in vascularization.[14] It was an enough period for demarcation area. The area of necrosis and the entire flap area were measured using a transparent acetate paper (grid method). Although all flaps were planned to be the same size, the ratio of the necrotic area to the flap was used as flap contraction of each rat may be different during the wound healing process. Thus, this ratio was used to avoid errors due to contraction during wound healing. The percentage values were calculated. (Figure 1)

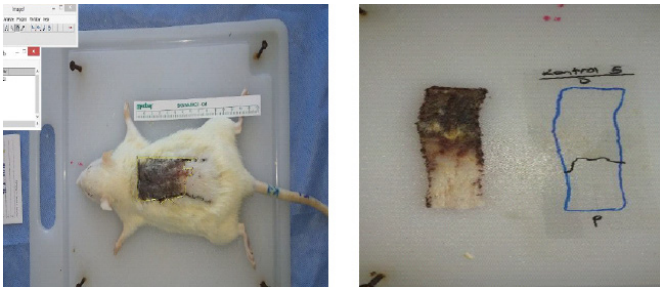

Figure 1: Clinical Evaluation of The Rats

Full thickness tissue samples taken from the transition zone between necrotic and intact tissue in the flaps of rats sacrificed on the 7th day were preserved under appropriate conditions. The transition zone was preferred because it has a tendency to necrosis or healing process. Tissue samples were fixed in 10% buffered formalin solution. They which were dehydrated by passing through graded alcohols were taken into xylene and kept until their transparency was completed. After 5 hours of liquid paraffin infiltration in a 60°C oven after clearing, the tissues were embedded in hard paraffin blocks. The blocks were kept in the refrigerator at +4°C. Before starting the cutting process, 4 µm sections were taken from the blocks, which were taken to -18°C, with a microtome. Sections were stained with Hematoxylin Eosin and

Mallory Azan histological stains. The sections were stained with Hematoxylin Eosin and Mallory Azan histological scales. Polymorphonuclear leukocyte and lymphocyte density, edema in the papillary dermis, extravasated erythrocytes, and edema in the reticular dermis were evaluated with scores from 0 to 4 according to their respective quantities. (Table 1)

Table 1: The Histopathologic Evaluation

	None	Few	Average	Dense	Very dens
Polymorphonuclear leukocyte and lymphocyte density	0	1+	2+	3+	4+
Edema in the Papillary Dermis	0	1+	2+	3+	4+
Extravasated Erythrocytes	0	1+	2+	3+	4+
Edema in the Reticular Dermis	0	1+	2+	3+	4+

Results

Overall, 14 rats survived and were evaluated. The groups were evaluated both clinical and histopathological results.

Clinical evaluation

The quantity of necrosis was different during the inspection. (Figure 2) Contraction developed in all flaps after 7 days postoperatively, and total flap surface area at 7th day between the two groups were statistically different. (p=0,005) The percentages determined after data from planimetric measurements and Image J program were compared between the ticagrelor and control groups, and it was found that in the ticagrelor group, flap necrosis rates were statistically lower than in the control group. (p=0,002) (Table 2)

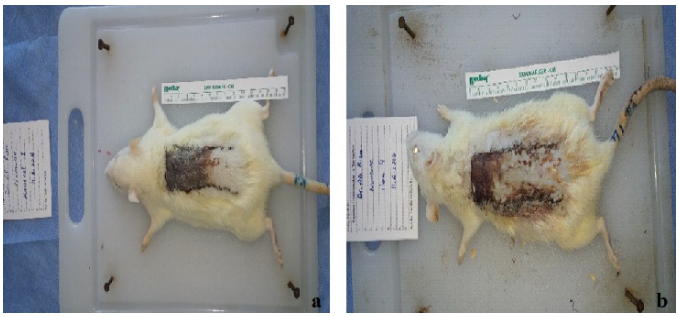

Figure 2.
a) One of The Control Group Rats at 7th Day.
b) One of The Ticagrelor Group Rats at 7th Day.

Table 2: Statistical Analysis of The Clinical Evaluation of The Clinical Evaluation

Group		n	Mean value	Standard deviation	Standard error	p value
Total surface area at 7th day (mm)	Control	7	2812,286	56,257	21,263	0,005
	Ticagrelor	7	2648,429	111,747	42,236	
Necrotic area (mm)	Control	7	1565,143	184,960	69,908	0,002
	Ticagrelor	7	859,286	375,815	142,045	

Histopathological evaluation

Inflammatory cells and necrosis were observed less frequently in the ticagrelor-treated group than in the control group. (Figure 3) However, no significant differences were observed between the histopathological scores of the groups. (Table 3)

Table 3. Statistical Analysis of The Histopathologic Evaluation

	Polymorphonuclear leukocyte and lymphocyte density	Edema in the Papillary Dermis	Extravasated Erythrocytes	Edema in the Reticular Dermis
Treatment group (n=7)	2.0	0.85	0.71	0.85
Control group (n=7)	2.71	1.0	1.0	1.0
p	0,255	0,317	0,287	0,299

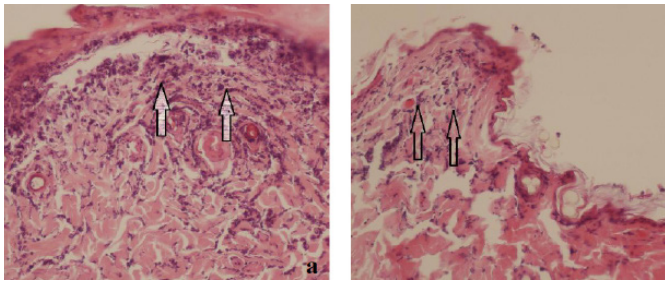

Figure 3: Polimorphonuclear Leucoyst Infiltration of The Control Group b) Less Intense PMNL Infiltration Was Observed in The Ticagrelor Group .

Discussion

In random pattern skin flaps, the blood supply is through the superficial plexus, and the flaps can be harvested using the 2:1 length:width ratio rule. As this ratio increases, the probability of necrosis also increases. When necrosis occurs, undesirable results, such as additional surgical interventions, increased hospital stay, and increased treatment costs, are encountered. In this context, it is clinically important to increase the viable part of the flap

by reducing ischemia-reperfusion damage that develops in the distal part of the random pattern flaps.[15,16]

As soon as the flap is harvested, vasoconstriction occurs owing to adrenaline, noradrenaline, thromboxane A², and prostaglandin F²α.[17] Afterwards, the perfusion of the flap decreases with the cutting of the surrounding vessels, and intravascular thrombosis formation increases owing to mechanical damage to the vascular endothelium. Platelet aggregation, intravascular thrombosis, and ultimately flap necrosis may occur in vessels with endothelial damage.[7,18] Therefore, vasodilators, antithrombotic agents, agents that prevent neutrophil aggregation and adhesion, anti-inflammatory agents, and antioxidant agents have been used.[19,20]

Ticagrelor is prescribed to reduce the risk of first myocardial infarction or stroke in patients with coronary artery disease at a high risk for these events, such as patients with type ² diabetes, to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome, and to reduce the risk of stroke in patients with acute ischemic stroke or high-risk transient ischemic attack.[21] However, various anticoagulant and antiaggregant agents have been studied to increase blood flow in skin flaps and prevent ischemia, but no previous study has examined the effect of ticagrelor in increasing the viability of random pattern flaps. In our study, the dose of ticagrelor was preferred considering the effective doses in studies on the inhibition of vascular smooth muscle contraction,[22] protection of the heart from reperfusion injury after myocard infarctus,[23] and reduction of platelet activation in diabetic rats.[24] However, further research can be conducted using variable doses and applications.

Compared to clopidogrel, ticagrelor has faster, more potent, and more consistent effects.[25] Studies have also shown that ticagrelor, which increases the plasma concentration of adenosine, is superior to clopidogrel in preventing no-reflow.[26] According to literature, the viability of random skin flaps in rats is increased by the use of clopidogrel. [6,27] In our study, necrotic area in the ticagrelor group was lower than low-molecular weigh heparin, combined therapy group and clopidogrel group in the study of Fatemi et al.[27] Our results showed that ticagrelor had a similar effect in improving the viability of random skin flaps.

Conclusion

We found a statistically significant difference in clinical outcomes with the use of ticagrelor. However, no significant differences were found in the histopathological observations. A limitation of this study is the fact that histopathological examination of the transition zone is a subjective. However, further research is required.

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Ethics Committee Approval:

The Decision Number of Local Ethical Committee approval at Ankara Universtiy Animal Experimentation Ethical Committee was 2016-9-101.

Conflict of Interest:

The authors declare no conflict of interest associated with this manuscript. can be shared on demand if any concern rises due to the reliability of the data but according to the ethical and legal regulations in Turkey the authors can not share the data via a data repository.

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RESEARCH ARTICLE

The Role Of Psychiatric And Demographic Factors In The Etiology of Hyperemesis Gravidarum

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Hyperemesis gravidarum, Depression, Anxiety, Rosenberg scale, Multidimensional perceived social support scale, The dyadic adjustment scale

Abstract

Introduction: Our aim in this study is to show how various aspects of the psychosocial health status and demographic features relate to the development and severity of hyperemesis gravidarum (HG). **Methods:** A total of 100 women before 20 weeks of pregnancy were enrolled in a study. The pregnant women were divided into three groups, hospitalized hyperemesis gravidarum patients, HG outpatients, and control group respectively. Pregnant women were questioned by scales after written consent. These scales were Rosenberg's self-esteem scale and multidimensional perceived social support scale and The Dyadic Adjustment Scale. SPSS 20.0 software (SPSS Inc., Chicago, USA) was used for analyses. Statistical significance was set at $p< 0.05$. **Results:** Duration of marriage significantly differs between hospitalized HG group and the control group ($p=0.045$), and between the HG group and the control group ($p=0.006$). Parity significantly differs for nulliparity between hospitalized HG and nonhospitalized HG groups with the control group. According to our data among all parameters, some (age, educational status of women and husband, types of family, economic status, previous history of depression, planned pregnancy, feeling of anxiety caused by pregnancy, having health insurance, working status, anxiety, and depression) were found not to be related **Conclusion:** Our study provides powerful scientific evidence of a psychogenic etiology by putting forth that psychological factors have no effect on the risk of HG.

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Introduction

Nausea and vomiting are very common symptoms (%50-80) in the first trimester of gestation. Prolonged and severe nausea and vomiting are called hyperemesis gravidarum (HG) .[1] HG symptoms can affect daily life, working quality, and social interactions.[2-3-4] Pregnant women may experience fatigue and burden from HG due to its nature, and concerns have been expressed about the advent of psychiatric disorders at this time of vulnerability.[5] Several research has stated that HG is predisposed to psychiatric illnesses, whereas others have argued that HG itself produces symptoms of posttraumatic stress disorder (PTSD), depression, and anxiety.[6] However, it is unclear whether psychiatric symptoms may also play a role in the pathogenesis of HG. Psychological status and low social support are commonly unheeded risk factors of HG. Psychosocial health is a complex structure, enclosing psychological and social areas such as depression, stress, self-sufficiency, and social support. It is already known that the prevalence of psychosocial health issues such as depression and anxiety, which negatively affect pregnant women and infants, rises throughout pregnancy. Depression prevalence among pregnant women was reported at 14.9%.[7]

Whether depression causes HG, or HG causes depression is still a controversial issue, and studies on this subject are lacking in the literature. Evaluating the risk factors and disease etiology for women has effects on counseling, particularly for the elevated percentage of women that revise reproductive plans (37%) due to their experiences with HG.[8] In this study, we aim to show how various aspects of the psychosocial health status and demographic features relate to the development and severity of hyperemesis gravidarum.

Material and Methods

The present study was conducted in the training and research hospital, a tertiary care center from May 2019 to October 2019. The study was approved by the local ethics committee (approval number: 2019/56) and was performed per the ethical standards described in the Declaration of Helsinki. All participants signed a written informed consent prior to the study.

The women before 20 weeks of pregnancy were enrolled in a study. The pregnant women were divided into three groups, hospitalized hyperemesis gravidarum, HG, and control group respectively. The gestational week was decided with an ultrasound and the last menstruation date. If there were more than 7 days of inconsistency between gestational weeks based on crown-rump length (CRL) and last menstrual period, a gestational week was decided according to CRL.

In all groups, the pregnant women's sociodemographic and clinical characteristics such as ages, parities, gestational weeks, etc. were questioned with a form at the admission to the hospital whether inpatient or outpatient clinics. HG was defined as repeated nausea and vomiting in early pregnancy, not due to other causes (e.g., gastroenteritis) with any of the following: inpatient admission, day stay with IV fluids, or vomiting associated with loss of 5% of her weight.[9] McCarthy FP, Khashan AS, North RA, et al.SCOPE Consortium A prospective cohort study investigating associations between hyperemesis gravidarum and cognitive, behavioral, and emotional well-being in pregnancy. PLoS One. 2011;6(11):e27678.). Women with hospitalized HG were considered as severe HG and set out as one of the study groups. Women with systemic disease or psychiatric disorders, antenatal bleeding, fetal anomaly, multiple pregnancies, and pregnant women with difficulty understanding the questions of scales in the present study were excluded from the study.

Measurements:

Pregnant women were questioned by scales after written consent. These scales were Rosenberg's self-esteem scale and multidimensional perceived social support scale and Dyadic Adjustment Scale. The pregnant women were evaluated by scales about the relation between self-esteem, social support, and perception of the relationship as a couple with HG.

The Multidimensional Scale of Perceived Social Support (MSPSS) was originally developed by Zimet et al. in 1988.[10] The scale Turkish validation was conducted and the MSPSS consists of 12 items including a subjective evaluation of the sufficiency of social support perceived from three sources (family, friends, and special person). The higher the score means the higher the perceived social support.[11]

Rosenberg Self-Esteem Scale (RSES) is developed to measure self-esteem. The 10-item RSE scale is used to assess self-esteem. The instrument was initially created to gauge high school students' self-esteem. Nonetheless, since its creation, the scale has been applied to a wide range of populations, including adults, for which norms are available.[12] The scale includes 10 items that are

rated on a 4-point Likert-type scale. Higher scores correlate to higher levels of self-esteem. The Turkish version was validated by Çuhadaroğlu.[13]

The Dyadic Adjustment Scale (DAS) assesses the quality of relationships as perceived by couples. A relationship's one or both partners may complete the 32-item DAS rating test, which is written at an eighth-grade reading level.[14] This scale was developed in 1976 by Spanier. Turkish validity and reliability study was conducted by Fışıloğlu and Demir in 2000.[15]

The DAS is composed of 32 items and 4 sub-dimensions; dyadic satisfaction, couples commitment, dyadic consensus, dyadic cohesion, and dyadic affectional expression respectively. The majority of items use a 6-point format, with options scored from 0 to 5, ranging from either always agree to disagree or all the time to never. The total score is the sum of all items, higher scores reflect a higher perception of the quality of the relationship.

Statistical Analysis:

Continuous variables are reported as mean ± SD for normally distributed data and median (interquartile range) for skewed continuous data. Categorical variables are declared as numbers (percentages). Kruskal-Wallis test and the chi-square test or Fischer's Exact Test were applied to compare continuous and categorical data study groups. One-way ANOVA post-hoc tests were used for subgroup analyses. Normality assumption was tested using Shapiro–Wilk test. SPSS 20.0 software (SPSS Inc., Chicago, USA) was used for analyses. Statistical significance was set at $p< 0.05$.

Results

The study included a total of 100 pregnant women of which 17 pregnant women (17%) were in the group with hospitalized HG patients (inpatients), 46 pregnant women (46%) were in the group with nonhospitalized HG (outpatients), and 37 pregnant women were formed the control group (37%). The sociodemographic and clinical characteristics of the study groups were presented in Table 1.

Table 1: Sociodemographic and clinical characteristics of study groups

	Hospitalized HG (N=17)	HG (N=46)	Control group (N=37)	*P*
	Mean± SD	Mean± SD	Mean± SD	
Age	27±5,1	26,7±4,3	28±5,1	0.441
Duration of marriage	4.1±3.7	4.3±3.5	6,84±4.4	**0.007[a]**
Age at marriage	22.9±3.4	22.4±3.7	21.2±3.3	0.172
	Median (IQR)	Median (IQR)	Median (IQR)	
Gestational week	9 (2)	8.5 (3)	8 (4)	0.375
Number of household members	3 (3)	3 (2)	3 (1)	0.405
	N (%)	N (%)	N (%)	
Parity				**0.035[b]**
Nulliparity	9 (52.9%)	23 (50%)	7 (18.9%)	
Primiparity	4 (23.5%)	14 (30.4%)	16 (43.2%)	
Multiparity	4 (23.5%)	9 (19.6%)	14 (37.8%)	
Types of family				0.467
Nuclear family	13 (76.5%)	38 (82.6%)	33 (89.2%)	
Extended family	4 (23.5%)	8 (17.4%)	4 (10.8%)	
Employed women	3 (17.6%)	8 (17.4%)	5 (13.5%)	0.873
Employed husband	14 (82.4%)	45 (97.8%)	34 (91.9%)	0.097
Education of women				
Primary/ secondary school	11 (64.7%)	16 (34.8%)	24 (64.9%)	**0.011**
High school/ university	6 (35.3%)	30 (65.2%)	13 (35.1%)	
Education of husband				
Primary/ secondary school	7 (41.2%)	22 (47.8%)	18 (48.6%)	0.867
High school/ university	10 (58.8%)	24 (52.2%)	19 (51.4%)	
Economic status				
middle income				
Adequate income				
Having health insurance	13 (76.5%)	40 (87%)	34 (91.9%)	0.294
Previous history of depression	3 (17.6%	4 (8.7%)	5 (13.5%)	0.586
Planned pregnancy	16 (94.1%)	44 (95.7%)	35 (94.6%)	0.960
The feeling of anxiety caused by pregnancy				0.610
No	4 (23.5%)	19 (41.3%)	14 (37.8%)	
A little	8 (47.1%)	15 (32.6%)	16 (43.2%)	
Yes	5 (29.4%)	12 (26.1%)	7 (18.9%)	

HG: hyperemesis gravidarum,

[a]Duration of marriage significantly differs between hospitalized HG group and the control group (p=0.045), and between the HG group and the control group (p=0.006).

[b]Parity significantly differs for nulliparity between hospitalized HG and HG groups with the control group

The scores of the Dyadic Adjustment Scale with subscales, the Rosenberg Self-Esteem Scale, and the Multidimensional Scale of Perceived Social Support with subscales by study groups of pregnant women were presented in Table 2.

Tablo 2: The scores of the Dyadic Adjustment Scale with subscales, Rosenberg Self-Esteem Scale, and the Multidimensional Scale of Perceived Social Support with subscales by study groups of pregnant women

	Hospitalized HG Mean± SD	HG Mean± SD	Control group Mean± SD	*P*
Dyadic Adjustment Scale				
Dyadic satisfaction	41,8±4,2	41,7±4,6	41,4±6,8	0.945
Dyadic Cohesion	57,9±6,4	53,8±9,7	56,5±8,2	0.173
Dyadic Consensus	15,7±4,3	13,6±5	14,9±5	0.250
Affectional Expression	10,6±1,4	9,9±2,1	10,3±2	0.415
Rosenberg Self-Esteem Scale	31,4±7,2	32,2±4,8	32,9±4	0.599
Multidimensional Scale of Perceived Social Support				
Special person	11,1±7,9	15±8,5	15,8±8,1	0.137
Family	24,7±4,2	24±5,8	25±5,3	0.670
Friends	20,1±7,5	20,1±7,1	20,1±7,5	0.832

HG: Hyperemesis gravidarum, SD: standard deviation

Due to our data among all parameters; age, educational status of the woman and her husband, types of families, economic status, previous history of depression, planned pregnancy, the feeling of anxiety caused by pregnancy, having health insurance, working status, anxiety, and depression were found unrelated. Parity and duration of marriage were found to be related. Duration of marriage significantly differs between hospitalized HG group and the control group (p=0.045) and between the HG outpatient group and the control group (p=0.006). Parity significantly differs for nulliparity between hospitalized HG and HG outpatient groups with the control group.

Discussion

The health problems that HG patients experience throughout pregnancy and because of their quality of life may be a factor in their psychiatric problems.

In the current study, sociodemographic characteristics and self-esteem, perception of social support, and couple relations were investigated with regard to effects on the HG. According to our data among all parameters, some (age, educational status of women and husbands, types of families, economic status, previous history of depression, planned pregnancy, feeling of anxiety caused by pregnancy, having health insurance, working status, anxiety, and depression) were found unrelated, whereas others (parity, duration of marriage) were found related.

The individual's degree of confidence was assessed using the Rosenberg Self-Esteem Scale (RSES). However, there was no connection between a person's level of confidence and the occurrence or seriousness of HG. The Dyadic Adjustment Scale (DAS) measures how couples perceive the quality of their relationships. In our study when compared, the duration of marriage significantly differs between hospitalized HG group and the control group (p=0.045), and between the HG group and the control group (p=0.006). Parity significantly differs for nulliparity between hospitalized HG and HG groups with the control group. Anxiety and depressive symptoms were not different between HG patients and the control group in this study.

It is well known that parity rises with marital longevity. Since nulliparity is a recognized risk factor for HG, parity and the length of the marriage may serve as dependent variables. Hence, rather than psychological issues, the length of the marriage and the number of children are more likely to be dependent variables.

Our study has limitations, especially since the number of patients is limited and the subjects are not randomized from the whole population of HG sufferers. However, the results of this study have inferences for counseling.

Shorter overnight sleep durations and several daytime dysfunctions were detected, especially in the HG group, according to research by Yıldırım and colleagues. These outcomes may be a result of the mental health conditions of the individuals or their symptoms of nausea and vomiting.[16] In a study done in 2017, it is shown that not only depression but also anxiety disorders were more common among patients with HG compared to the control group.[17]

Most women with HG have no psychological diagnoses before HG development during pregnancy. The etiology of HG is unknown and studies still focus on psychiatric causes although the fact that this hypothesis has never been scientifically proven and most studies refute it.[18] In a study made in 2021, 60

pregnant women diagnosed with HG in the first trimester of their pregnancies, and 97 healthy pregnant women with characteristic features as the HG group were compared in terms of psychological resilience and anxiety levels. They detected no significant differences between the groups in terms of anxiety levels. Psychological resilience was measured using the Resilience Scale for Adults, and there was a significant difference between the groups.[19] Simpson et al. Found that pregnant women with HG scored significantly higher on the scales related to conversion disorder (p values <0.01) than did a control group. But there were no significant differences among HG women and the control group after their pregnancy.[20] D'Orazio et al. did not find any evidence for a psychosomatic etiology and association between HG and personality. Based on the findings of this pilot investigation, pregnant women with mild to moderate levels of NVP are no more likely than those without it to experience higher psychiatric problems. On the other hand, in terms of personality and psychological traits, women with HG were comparable to pregnant women with normal levels of NVP.[21]

There are no factors that have been clearly defined to increase the risk of HG including depression and anxiety symptoms. The Depression scale is high in women with HG and it is still a matter of debate which is the cause and which is the result. Unfortunately, an emphasis has been placed on the theory of psychiatry as the etiological factor of HG in the past, which was not supported very much by the current literature. Psychiatric disorders HG patients experience could be a result of HG's complicated pregnancy. The psychological theory that describes the pathogenesis of HG puts forward that the presence of conversion or somatization disorder or a patient's exaggerated response to stress can cause HG.[17] Although it is incorrectly assumed that emotional anguish causes HG, it is secondary to the extreme pain that it causes.[22]

In a study by Magtira et al., the psychological sequelae related to HG are found to be presumably the outcome of physical symptoms such as severe nausea and vomiting, medication, and hospitalization, and probably have no role in the etiology of the disease.[8]

In our study, we haven't found evidence to support that HG may have psychogenic etiology. Although the etiology of HG is not fully defined, we believe that physiological and genetic aspects may be more thoroughly identified. In this context, it may be more useful to conduct research in this direction.

Conclusion

In our study, we concluded that the duration of marriage reduces the risk of developing HG. Parity which is a known risk factor of HG increases with the duration of the marriage. The healthcare provider needs to understand the etiology of HG and it has effects on counseling. The effect of genetic factors in HG is becoming more and more clear It became more and more apparent that there is a genetic component of HG.[23] HG is not an enough studied condition of enough pregnancy that causes both short-term maternal physical and mental health problems. Besides, it may potentially result in lifetime effects on the fetus.[24] Considering this situation, analysis and prevention of HG etiological risk factors are important. According to the analysis we conducted and the conclusion we came to; although mistakenly believed to be the root of HG, depression and anxiety are secondary to the extreme misery induced by the condition. Our study provides powerful scientific evidence of a psychogenic etiology by putting forth that psychological factors do not affect the risk of HG.

Disclosures:

The authors declared no conflict of interest.

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RESEARCH ARTICLE

The Need for Emergency Case Management in Family Medicine: A Capital City Case

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Abstract

Introduction: The aim of this study is to evaluate 112 emergency ambulance calls made from primary healthcare institutions and to determine the reasons for patient referrals, the most frequent (pre)diagnoses they received according to age groups, and the frequency of encounters with these patients. Additionally, the study aims to identify which topics should carry more weight in family medicine specialty education and in-service training for individuals working in family health centers. **Methods:** Our study is a retrospective cross-sectional and descriptive study. Between November 2018 and November 2019, we retrospectively reviewed 112 emergency ambulance requests from family health centers in Ankara using the 112 command and control center archive records of the relevant patients. A total of 1829 calls were evaluated. Various parameters such as age, gender, vital signs, urban/rural case status, reason for the call, type of call termination, the ICD-10 diagnostic code, and ambulance type were analyzed. **Results:** Among the patients, 45.54% were female. The mean patient age was 47.31±24.62 years. The most frequent triage code assigned to patients was code yellow, accounting for 46.36% of cases. While 33.95% of patients were referred due to cardiovascular diseases, 12.52% for trauma, 7.22% for gastrointestinal diseases, and 6.62% for pulmonary diseases. Trauma and fever were more prominent in pediatric cases. Among diagnoses in the geriatric age group, vertigo was identified as one of the top five diagnoses. **Conclusion:** Medical reasons constituted the most common causes for 112 emergency ambulance requests, and the primary method of resolution by 112 teams was hospital transfer. Through this study, we identified the primary care physician's most frequent involvement in emergency case management and areas where they require assistance. A majority of the relevant cases were assigned code yellow, indicating that reinforcing family health centers could provide a solution to alleviate unnecessary patient overcrowding in emergency departments.

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Introduction

Family physicians constitute the first point of medical contact to the health system; provide an open and unrestricted access to those who wish to receive services; deal with all health problems regardless of age, gender or any other characteristic of the individual; and manage acute and chronic health problems of patients simultaneously.[1] Individuals apply to FHCs (Family Health Centers) at a time when their ailments have not yet been defined and differentiated. Family medicine specialists identify diseases with their unique problem-solving skills and perform important services in its management and coordination.[1] For this reason, rotations in the curriculum of family medicine specialty training are important.[2] During these rotations, trainees are taught when and how much intervention should be made in various diseases, how to detect emergency situations and when they should be referred. With this study, it is aimed to make important determinations about which subjects should be included more in the current curriculum in rotations of family medicine specialty education and in emergency situations. As a matter of fact, there is not a sufficient number of studies in the literature on the diseases for which patients are mostly referred from family health centers by 112 Emergency Ambulance service.

Based on this need, in our study, it was aimed to evaluate 112 emergency ambulance calls made from all Family Health Centers in Ankara, the capital of Turkiye, within a year and to determine the patients referred by 112 emergency ambulance as a result of these calls, the reasons for referral, the age groups in which the first interventions were made and how often they were referred due to which problems.

Material and Methods

Our study is a retrospective cross-sectional and descriptive study. We retrospectively screened 112 emergency ambulance requests (n:1829) from all family health centers (n:345) in Ankara between November 1, 2018 and November 1, 2019 from the archival records of the relevant patients on a case-by-case basis. Records before the Covid 19 pandemic period was chosen in the hopes to reflect more accurate social data.

Our study was based on calls made from all family health centers in the capital city within one year between the relevant dates and the records kept by the 112 Command and Control Center through the relevant teams of all patients who were evaluated, referred or intervened through 112 Emergency Health Services. All age groups were included in the study, and cases outside the province of Ankara and patients who did not receive 112 Emergency Ambulance Health Service were excluded from the study.

Data Collection Tools

Some parameters such as age, gender, vital signs (consciousness, pupils, respiration, skin, pulse), urban/rural case status, reason for the call, the way it was terminated, prediagnosis(es) received (ICD10 diagnostic and superdiagnostic codes and names), type of the ambulance sent were analyzed.

Statistical Analysis

Among the descriptive statistical data, continuous variables were expressed as mean ± standard deviation and discrete data were expressed as number and %. SPSS 23 package program was used in the evaluations.

Research Authorization

The relevant records were anonymized by numbering the patients without including personal records. Ethics committee approval was obtained from the local ethics committee, and research permission was obtained from the relevant institution.

Results

In this study, a total of 1829 calls made by family physicians working in primary health care organizations in Ankara province were evaluated. While 43.63% (n=798) were male and 45.54% (n=833) were female, 10.83% (n=198) of the patients who received 112 emergency ambulance calls did not have their gender specified in the records. Of the patients, 25.97% (n=475) were over the age of 65, 48.11% (n=880) were between the ages of 18-64, and 15.09% (n: 276) were under the age of 18. The age of 10.83% (n=198) of the patients was not recorded and the mean age of the patients was 47.31±24.62 (minimum: 1; maximum: 96).

When the locations of the family health centers where the calls were made were examined, it was seen that the most frequent application was from Keçiören district, which is located in the center of the capital city, with 15.58% (n=285) and the least application was from Güdül district, which is located in a rural area, with 0.05% (n=1).

Regarding the vehicles that responded to the calls, 98.57% (n=1803) were panel-type ambulances, followed by 0.87% (n=16) snow-tracked ambulances, 0.16% (n=3) intensive care ambulances or obese patient panel vans, 0.16% (n=3) pa-

nel vans with four stretchers and 0.05% (n=1) motorcycle ambulances. While 97% (n=1775) of all calls were command-approved, 3% (n=54) were from 112 Emergency Health Stations that can work integrated with family health centers without command approval. While 57.30% (n=1048) of the applications were within the 112 teams' own regions, 42.59% (n=779) were outside their own regions.

Table 1 shows the data that the reasons of the calls were recorded in general and not on a diagnostic basis. The most common reason for emergency calls was medical reasons (84.53%, n=1546), followed by "other accidents".

Table 1: Main reasons for 112 emergency ambulance request calls made by family physicians working in primary healthcare

	n	%
Medical	1546	84.53
Other accidents	165	9.02
Injuries	44	2.41
Traffic accident	30	1.64
Other	25	1.37
Suicide	6	0.32
Health Measures	6	0.32
Work accident	4	0.22
Fever	2	0.11
Total	1828	99.94
Cause unknown	1	0.06
Total	1829	100.00

Detailed information on how 112 emergency ambulance calls made by family physicians working in primary healthcare organizations were finalized by 112 teams is given in Table 2.

Table 2: The manner in which 112 emergency ambulance calls made by family physicians working in primary care are concluded by 112 units

	n	%
Transportation (to hospital)	1565	85.57
Mission cancellation	172	9.41
Transfer - Rejection	63	3.44
Transport by another vehicle	20	1.09
On-site intervention	5	0.27
Other	2	0.11
Ex (Left in place)	2	0.11
Total	1829	100.00

While the most common type of finalization was "transfer", it was also found that the reasons such as "need for intensive care, lack of free space, need for medical equipment, need for specialist physicians, patient request, need for advanced specialized physicians" were shown in the detailed information recorded.

When the classification of all cases for which 112 emergency ambulance calls were made by family physicians working in primary health care organizations according to ICD diagnosis type, it was seen that CVS (Cardio-Vascular System) diseases were the most common with 33.95% (n=621). The lowest number of cases was found to be electric shock with 0.11% (n=2). Table 3 shows the classification of cases according to ICD diagnosis types in detail.

Table 3: Classification of cases called for 112 emergency ambulance by family physicians working in primary health care according to ICD diagnosis types

	n	%
Cardiovascular system diseases	621	33.95
Trauma	229	12.52
Gastrointestinal system diseases	132	7.22
Respiratory System	121	6.62
Neurological	84	4.59
Poisoning	65	3.55
Vertigo	56	3.06
Psychiatric	46	2.52
Pain	37	2.02
Fever	35	1.91
General symptoms and other signs	34	1.86
Other	34	1.86
Metabolic disorders	32	1.76
Genitourinary system diseases	24	1.31
Headache	18	0.98
Obstetrics or pregnancy	18	0.98
Epistaxis	14	0.77
Allergic conditions	13	0.71
Infectious diseases	8	0.44
Battered	7	0.38
Electric shock	2	0.11
Total	1630	89.12
Unclassified	199	10.88
Total	1829	100.00

In addition, 46.36% (n=848) of the cases were given code yellow, while 4 cases were given code black by 112 teams. While 69.38% (n=1269) of the cases were found to be conscious, 0.71% (n=13) were found to be completely unconscious. The details of triage and vital status of the examined cases are given in Table 4.

Table 4: Some examination results of 112 Emergency Ambulance Calls by family physicians working in primary health care organizations

		n	%
Triage	Code Yellow	848	46.36
	Code Green	656	35.87
	Code Red	124	6.78
	Code Black	4	0.22
	Missing	197	10.77
	Total	1829	100.00
Consciousness	Open	1269	69.38
	Closed	13	0.71
	Confuse	5	0.27
	Blurred	6	0.33
	Missing	536	29.31
	Total	1829	100.00
Pupils	Normal	1195	65.34
	Isochoric	34	1.86
	No Reaction	7	0.38
	Myotic	3	0.16
	Fix Dilated	4	0.22
	Midriatik	1	0.05
	Anisochoric	2	0.11
	Missing	583	31.88
	Total	1829	100.00
Respiration	Regular	1201	65.66
	Irregular	27	1.48
	Dyspnea	26	1.42
	None	11	0.60
	Fast	2	0.11
	Missing	562	30.73
	Total	1829	100.00
Skin examination	Normal	1176	64.30
	Pale	29	1.59
	Sweaty	18	0.98
	Cyanotic	11	0.60
	Hyperemic	4	0.22
	Dry	2	0.11
	Missing	589	32.20
	Total	1829	100.00
Pulse	Regular	1198	65.50
	Arrhythmic	39	2.13
	None	13	0.71
	Filiform	4	0.22
	Missing	575	31.44
	Total	1829	100.00

*Code yellow: Unstable condition; Code green: Stable condition; Code red: Critical emergency; Code black: Death

In addition, ICD diagnosis types were also determined according to age groups and the first five diagnoses among the most frequently diagnosed diseases are summarized in Table 5. In addition, the listed practice competencies expected to be acquired by the specialist physician and other complementary "core competencies" acquired during his/her education as specified in the Core Curriculum of Family Medicine Residency Training of the Board of Medical Specialization Curriculum Formation and Standard Setting System (TUKMOS) were defined as four levels.[2] The distribution of the relevant diagnostic codes according to the levels specified in the explanations section of Table 5 is also given. Accordingly, while the most common diagnostic code in children was "Trauma", it was determined that "CVS diseases" were the most common diagnostic code in adult age groups, and the competency level of both diagnostic codes was determined as 3 (refers to the level of applying intervention in non-complex, common typical cases). Here, while the competency of "Soft Tissue Trauma" is expected to be possessed by the specialist physician with a competency level of 3, it was also determined that it is specified as 2 competency levels under the sub-competency title of "Initial Assessment and Stabilization of Trauma Patient" in the relevant curriculum.

Table 5: Distribution of ICD diagnoses by age groups (Top 5 most common diagnoses) and level of competency in specialty curricula

Age range	Diagnoses	n	%	Competency Level
65 years and older	CVS diseases*	247	52.00	3
	Respiratory system diseases	52	10.95	2,3
	Trauma	45	9.47	2,3
	GIS diseases*	24	5.05	3
	Vertigo	20	4.21	-
18-65 age range	CVS diseases	350	39.77	3
	Trauma	102	11.59	2,3
	GIS diseases	83	9.43	3
	Respiratory system diseases	45	5.11	2
	Neurological diseases	37	4.20	2
Under 18 years old	Trauma	81	29.35	2,3
	Neurological diseases	36	13.03	2
	GIS diseases	25	9.06	3
	Fever	24	8.70	3
	CVS diseases**	23	8.33	3
	Respiratory system diseases**	23	8.33	2,3

*CVS: Cardiovascular system, GIS: Gastrointestinal system
**Diagnoses in equal proportions are also shown
***Four levels are defined for speciality competencies:
1: It refers to the level of having knowledge about how the initiative is carried out and being able to make explanations when necessary.
2: Refers to the level of being able to perform this intervention in an emergency, under guidance or instruction, or under supervision and control.
3: It refers to the level of being able to apply the intervention in uncomplicated, common, typical cases.
4: Refers to the level of ability to perform interventions in all types of cases, whether complex or not.

Discussion

With our study, we determined the reasons for referral of patients who were referred through 112 Emergency Health Services from all Family Health Centers providing primary health care services in a capital city within a year, the age groups for which problems they were referred, the frequency of acute problems encountered, and the issues that they had difficulty in managing alone in terms of diagnosis, treatment or follow-up in primary care.

In our study, when we looked at the main reasons for getting calls, medical reasons were 84.53%, other accidents (other than traffic accidents) were 9.02%, and traffic accidents were 1.64%. In a thesis study, 112 diagnoses were evaluated and it was observed that the first rank was medical problems with 59.5%, the second rank was falls and occupational accidents involving falls with 23.2%, and the third rank was traffic accidents and multitrauma cases with 17.3%.[3] In a study conducted by Oktay et al. it was shown that the most frequent 112 calls were medical (57.5%), the second most common was traf-

fic accidents (21.6%) and the third most common was other accidents (7.56%).[4] In a study conducted by Özata et al. the reasons for admission to 112 Emergency Department were investigated and it was shown that the most common reason for admission was medical with a rate of 70%.[5] When we looked at the results, a similar result was obtained with our study, and it was observed that access to 112 Emergency Health Services was mostly for medical reasons. The fact that medical reasons are more frequent in FHCs can be explained by the fact that the number of chronic diseases increases with age in the area where the study was conducted, and the possibility of emergencies caused by these diseases increases.

In our study, patients were referred for CVS diseases, trauma, gastrointestinal, pulmonary and neurological reasons, respectively. In another study examining the factors affecting the practices of primary care physicians regarding emergencies, it was reported that approximately 62% of the participants felt that CVS and central nervous system emergency management should preferably be given as applied training in the emergency department of the hospital.[6] This study and our study show us once again the importance of Emergency and Cardiology rotations, which are mandatory in the curriculum of family medicine specialty training. In these rotations, the necessity of intensifying trainings especially on the management of CVS diseases in primary care has been revealed. After CVS diseases, it has been determined that trauma patients are referred the most, especially in the pediatric age group, and it is important that the management of trauma patients in primary care in family medicine specialization training is covered during the Emergency rotation in order to train competent family medicine specialists in this field.

In our study, almost half of the patients were given a yellow code, more than one third were given a green code, and very few were given a red or black code in 112 ambulance triage. In another study, when the triage codes of patients admitted to the pediatric emergency department were examined, it was found that 62.3% (n=498) of the codes were green, 35.6% (n=285) were yellow, 0.8% (n=6) were red and 1.4% (n=11) were forensic, which shows us that emergency departments are used unnecessarily with undifferentiated patients.[7] The fact that code green was lower than code yellow in our study shows that family physicians have an important role in reducing unnecessary visits to the emergency department. However, code green having a significant rate suggests that it would be appropriate to strengthen the primary health care system (education, facilities, etc.). In a study conducted by Edirne et al. 22.1% of the patients admitted to the emergency department had applied to a family health center before coming to the emergency department.[8] The most common reasons for presentation were related to the digestive system, nervous system and musculoskeletal system (27.7%, 24.6% and 11.0%, respectively).[8] In a thesis study, it was observed that 42.3% of the patients consulted the family physician before going to the pediatric emergency department and 27.4% of the patients who applied to the pediatric emergency department were referred by the family physician. In the same study, when the reasons for presentation to the pediatric emergency department were evaluated on the basis of ICD diagnostic codes, it was observed that 41.5% of the patients received a diagnostic code of J (respiratory system diseases) and 39.5% received a diagnostic code of R (symptoms and abnormal clinical and laboratory findings)[7]. In a study by Afilalo et al. it was stated that 75% of semi-urgent and 70% of non-urgent patients admitted to the Emergency Department were followed up by the physician in charge of primary health care. In the same study, 22% of non-urgent patients and 27% of semi-urgent patients had consulted a primary care physician before presenting to the Emergency Department. In this study, accessibility was found to be the reason for the low number of applications to primary health care providers in 32%, perception of need in 22%, referral/follow-up to the Emergency Department in 20%, familiarity with the Emergency Department in 11%, trust in the Emergency Department in 7%, and the reason was not clear in 7%.[9] Studies showing that patients apply to FHCs before coming to the emergency department reveal an important situation. It indicates that a strong primary healthcare service provision will increase the functionality and efficiency of the healthcare system. As more opportunities for diagnosis and treatment are provided for patients who apply to FHCs, the rate of emergency department visits will decrease. In our study, more than half of the pediatric patients referred by 112 Emergency Service ambulance from FHCs were due to trauma, neurological causes and GIS (Gastrointestinal System) diseases. While fever was the fourth most common reason, CVS diseases and respiratory system diseases were the fifth most common reasons for referral. When our study and the

studies in the literature are evaluated together, patients frequently apply to FHC; the fact that primary health care is easily accessible and that family medicine specialists provide comprehensive and continuous health care services to each individual without discriminating age, gender and disease makes family medicine specialists the first physicians to whom patients apply. It is important to strengthen the physicians working in FHCs on CVS diseases, GIS diseases, neurological diseases and respiratory system diseases. Primary care physicians should also be informed about the management of trauma patients for all patients, especially pediatric patients. In our study, pediatric patients were mostly referred for trauma. Trauma was followed by neurologic diseases, GIS diseases, fever, CVS diseases and respiratory system diseases.

In our study, when referrals were evaluated according to the age group of the cases, patients over the age of 65 were referred 52.00% for CVS diseases and 10.95% for respiratory system diseases, patients between the ages of 18-64 were referred 39.77% for CVS diseases and 11.59% for trauma, and patients under the age of 18 were referred 29.35% for trauma. While it was found that trauma and symptoms such as fever were more prominent in pediatric cases, it was found that vertigo was among the first five diagnoses in addition to the geriatric age group diagnoses, but it was observed that there was no competency level to be acquired for this disease in the curriculum of family medicine specialty training.[2] In a thesis study, 112 diagnoses were evaluated, and it was observed that patients over the age of 18 were mostly diagnosed with CVS diseases at a rate of 24.2%, falls or occupational accidents at a rate of 18%, and falls at a rate of 52% in patients under the age of 18.[3] Similar results were observed in our study, and it was found that patients under the age of 18 were more likely to be diagnosed with trauma, falls or other accidents, whereas patients over the age of 18 were more likely to be diagnosed with CVS diseases. Diagnoses of chronic diseases increase with advancing age. One of the most common chronic diseases is CVS diseases. As a matter of fact, according to the data of the Republic of Türkiye Ministry of Health Health Statistics Yearbook 2021, Ischemic Heart Disease ranks first among the Top 10 causes of YLL (Years of Life Lost) in 2019, and when the years 2002 and 2019 are compared, it is seen that this situation has an increasing trend.[10] Again, in our study, when evaluated separately in patients over 65 years of age, we see that the rate of diagnosis of CVS diseases is 52% and is higher than in other age groups. In a study by Dündar et al. evaluating the use of the Emergency Department in the age group of 65 years and older, it was found that the most common reason for presentation was cardiac diseases (40.5%).[11] When this study and our study are evaluated, the fact that admissions due to CVS diseases in the age group of 65 years and over are at the first frequency reveals the importance of follow-up and treatment of CVS diseases in this age group. At this point, person-centered care, which is one of the core competencies of family medicine specialty, comes to the fore, and longitudinal approach to patients and ensuring continuity in care gain importance.[1] For healthy aging of patients, the importance of periodic health follow-ups in family medicine specialty education is once again seen. For this purpose, Geriatric Monitoring and Evaluation was addressed as a separate topic within the framework of the Disease Management Platform (DMP) in FHCs in Turkiye and it was aimed to follow up each geriatric patient.[12] Recently, a center under the name of "YAŞAM" (LIFE) has been designed to ensure the healthy aging of the geriatric population. LIFE is planned to be situated in various regions integrated with the Geriatrics and Home Health Services department of hospitals.[13] All these contribute to ensuring more careful follow-up of this age group.

Limitations of the Research

The lack of sub-heading details of ICD diagnostic codes may have caused some data to be lost. 112 ambulance archive records may have caused incomplete information based on records in this study. The registration information of the relevant patients in the FHCs was not accessed and conducting the study only through 112 ambulance records may have caused possible data losses or inaccuracies due to the lack of data reliability, i.e. confirmation.

Conclusion

According to our study, 112 emergency ambulance was requested from FHCs for patients of all age groups mostly due to CVS diseases, trauma, GIS diseases, respiratory system diseases and neurological diseases, and it was determined that these patients were mostly referred. When the reasons for 112 emergency ambulance calls for patients under 18 years of age were evaluated, trauma, neurological diseases, GIS diseases, fever, CVS diseases and respiratory system diseases were observed respectively.

When the emergency triage codes of the cases in our study were evaluated, it was determined that 112 emergency ambulance was requested mostly for patients with yellow code, that is, unstable patients. The fact that the majority of the cases from family health centers were patients with Yellow and Red codes showed us that 112 emergency ambulance health service was used appropriately.

The contribution of family physicians to emergency health services is very important. When primary health care services are strengthened and patients' use of primary health care services is increased, it is predicted that the rate of emergency room visits can be reduced. Reducing unnecessary visits to emergency departments is of vital importance for truly emergency patients. In this regard, FHCs are expected to assume an important role and family medicine specialists should be more competent in the identified emergency case management issues. Family Medicine specialty training is an important and good opportunity for physicians to update their knowledge on needed topics. With an improved curriculum, it will be possible for family physicians to become more competent, and we think that this will further increase professional satisfaction and prestige, which are stated as the reasons for choosing family medicine.[14]

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RESEARCH ARTICLE

Genetic Ethiology, Associated Anomalies in Fetal Aberrant Right Subclavian Artery: A Retrospective Cohort Study in a Tertiary Hospital

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Abstract

Introduction: This study aimed to determine the prevalence of chromosomal anomalies in fetuses with isolated and non-isolated aberrant right subclavian artery (ARSA) and to evaluate its association with other congenital anomalies. **Methods:** From 1 June 2021 to 1 June 2023, 47 ARSA cases were diagnosed by prenatal ultrasound in our hospital. The fetuses were divided into isolated ARSA group and non-isolated ARSA group. Among the 47 fetuses, 15 were characterized in the isolated group and 32 with combined other ultrasonic abnormalities in the non-isolated group. General information, ultrasound presentation, chromosomal findings, and birth and pregnancy outcomes were reviewed retrospectively. **Results:** In the non-isolated ARSA group, 17 cases (53,1%, 17/32) were associated with congenital heart defects, and 8 cases (25 %, 8/32) were associated with extracardiac abnormalities. Chromosome karyotype analysis was performed successfully with all 23 samples, and a total of 8 abnormalities (17 %, 8/47) were detected, including 7 cases of trisomy 21, and 1 case of trisomy 18. Single-nucleotide polymorphism array was performed in these 5 cases. Microdeletion was detected in four cases, but one of the arrays was reported normal. Using SNP-array and karyotype analysis in fetuses with ARSA, the total chromosomal anomaly detection rate was found 25.5 % (12/47). **Conclusion:** The most common malformation accompanying ARSA is cardiac abnormality. Isolated ARSA has a low risk of chromosomal abnormalities, so invasive chromosomal testing is not recommended. Non-isolated ARSA has a high incidence of chromosomal abnormalities, so early karyotyping should be recommended.

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Introduction

Aberrant right subclavian artery (ARSA) is a congenital anomaly of the aortic arch that can be seen in approximately 2 % of healthy individuals.[1,2] ARSA may be part of a complex heart malformation or genetic syndrome or a normal vascular variation. Normally, the right subclavian artery arises from the brachiocephalic trunk. In contrast, ARSA originates superior part of the descending aorta and distal to the left subclavian artery. ARSA becomes the last branch of the aortic arch and passes behind the esophagus and trachea to the right arm. The aberrant artery forms a U-shaped loop with the descending aorta. Due to this structural anatomical difference, ARSA may press on the neighboring structures of the trachea and esophagus in newborns or infancy, and may cause many symptoms including dysphagia, respiratory distress, and stridor.[3,4]

Owing to the advances in prenatal ultrasound diagnosis techniques employed, an increasing number of fetal structural malformations are being diagnosed. These advances can help clinicians create effective diagnosis and treatment plans, reduce adverse pregnancy outcomes, and prevent birth defects.[5] Fetuses with ARSA are at high risk for trisomies and copy number variation (CNV) and prenatal ultrasound can accurately diagnose fetal ARSA.[6, 7, 8] In this study, we aimed to analyze and provide information on the relationship between genetic etiology, postnatal outcomes, and prognosis of ARSA associated with isolated and/or complex anomalies.

Material and Methods

Clinical data for patients who presented to the Turkish Ministry of Health Ankara Bilkent City Hospital at the Perinatology Clinic with ARSA during ultrasound examination between 1 June 2021 and 1 June 2023 were evaluated retrospectively. The present study protocol was approved by the institutional ethics committee in suitability with the principles of the Declaration of Helsinki and approved by Ankara City Hospital Clinical Ethics Committee (Date: 21-06-2023, Number: E2-23-4352). Pregnant women with multiple pregnancies, and perinatal outcomes unknown were excluded from the study. After the participants signed the informed consent form, chorion villus sampling, amniotic fluid, or cord blood was collected for karyotype analysis and/or single nucleotide polymorphism (SNP) array based on different gestational weeks. Prenatal other cardiac and/or other ultrasound abnormalities in fetuses were collected. The cases were divided into the isolated ARSA group (n=15 cases) and the non-isolated ARSA (ARSA combined with other ultrasonic abnormalities) group (n=32 cases). All ultrasonographic measurements were performed by at least two perinatologists while the patient was looking. Fetal ultrasonography examination of all participants was evaluated using Voluson E10 (GE Medical Systems) ultrasonography device and a 3.5 MHz convex transducer (GE C2-9-D) transabdominal probe was used for the measurements. Evaluations were carried out in accordance with practice guidelines.[9],[10] ARSA leaves the descending aorta, the junction of the aortic arch and the ductal arch, passes between the trachea and the vertebrae, and extends towards the right shoulder. Ultrasonic view of fetal ARSA is shown in Figure 1. Pregnancy outcome and postnatal development of all cases with ARSA were followed from hospital records and/or by telephone.

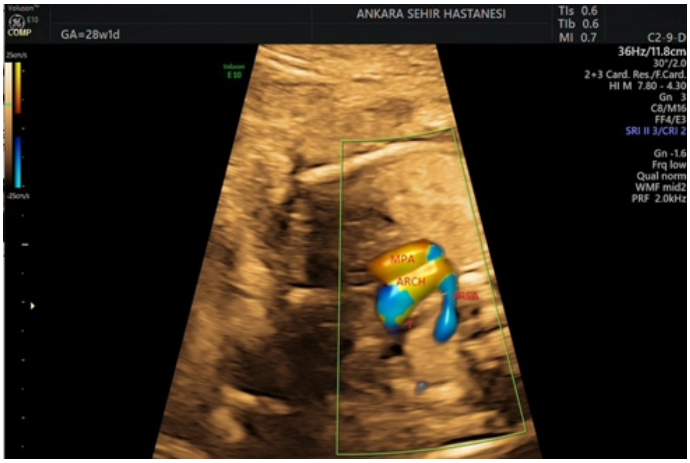

Figure 1. Ultrasound View of Fetal ARSA
Abbreviations: ARSA, aberrant right subclavian artery; MPA, main pulmonary artery; ARCH, aortic arch; T, trachea.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS v. 25, IBM, SPSS for Windows, NY: IBM Corp.). Categorical variables are presented in numbered and percentages.

Results

The fetuses were divided into isolated ARSA group and non-isolated ARSA group. Among the 47 fetuses, 15 were characterized in the isolated group and 32 with combined other ult-

Table 1. Fetuses with non-isolated ARSA (n=32)

Classification	Number of fetuses
Intrauterine Growth Restriction	1
Polyhydramnios	1
Urogenital System	
Hypospadias	1
Crossed fused renal ectopia	1
Combined with Congenital Heart Defects	
Ventricular septal defect	7
Left aortic arch	1
Right aortic arch	1
AVSD	1
TGA	1
DORV	1
Thymus hypoplasia	3
HLHS	3
Mitral dysplasia	2
Interrupted aorta	1
Anevrisma of foramen ovale	1
Ultrasonographic soft markers	
Renal pyelectasis	3
Choroid Plexus Cyst	4
Single umbilical artery	3
Echogenic Cardiac Focus	3
Clinodactyly	1
Central Nervous System	
Corpus callosum agenesia	1
Cavum vergae	1
Ventriculomegaly	2
Congenital Diaphragmatic Hernia	3
CPAM	1
Cleft lip	1
Omphalocele	1
Umbilical cord cyst	2
Eosophageal atresia	1
Pleural effusion	2
Gastrointestinal duplication cyst	1

Abbreviations: ARSA, aberrant right subclavian artery; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; CPAM, congenital pulmonary airway malformation.

rasonic abnormalities in the non-isolated group.

In the non-isolated group, 17 cases (53,1%, 17/32) were associated with congenital heart defects, and ARSA.[8] cases (25 %, 8/32) were associated with extracardiac abnormalities. Fetuses with extracardiac anomalies were associated with diaphragmatic hernia in 3 cases, congenital pulmonary airway malformation (CPAM) in 1 case, eosophageal atresia in 1 case, corpus callosum agenesia in 1 case, hypospadias and crossed fused renal ectopia in 1 case, and gastrointestinal duplication cyst in 1 case. It was together with other ultrasonographic soft markers in 7 cases (21.8 %, 7/32). The most common anomaly in fetuses with congenital heart defects is ventricular septal defect (14.8 %, 7/47) (Table 1).

In the non-isolated group, 6 patients terminated the pregnancy. Pregnant women numbered 1 and 11 shown in Table 2, gestational week at birth was 31 and 34 weeks of gestation, respectively. Other pregnant women's gestational week at birth were at the term, and the primary cesarean section rate was 25% (8/32). On the other hand, the gestational week at birth of all pregnant women in the isolated group was at term, and the primary cesarean section rate was 26% (4/15).

Chromosome karyotype analysis was performed successfully with all 23 samples, and a total of 8 abnormalities (17 %, 8/47) were detected, including 7 cases of trisomy 21, and 1 case of trisomy 18 (Table 2).

Normal chromosomal karyotype analysis was reported in 12 cases in the non-isolated group. SNP array was performed for 5 of these fetuses. 22q11.2 deletion was reported for 3 cases (3/5), 11q24.2q25

Table 2. Karyotype analysis detected in fetus with ARSA

Case	Karyotype analysis(CNV)	SNP-Array	Ultrasonic phenotype	Perinatal outcomes
1	47, X*, +21		ARSA, pleural effusion, ventricular septal defect	Postnatal exitus
2	47, X*, +21		ARSA, complet atrioventricular septal defect	Postnatal exitus
3	47, X*, +21		ARSA, bilateral clinodactyly, cavum vergae, perimembranous ventricular septal defect	TOP
4	47, X*, +21		ARSA, absent nasal bone, hyperechogenic cardiac focus, ventricular septal defect	TOP
5	47, X*, +21		ARSA, absent nasal bone, hyperechogenic bowel, single umbilical artery	TOP
6	47, X*, +21		ARSA, complete atrioventricular septal defect, umbilical cord cyst, umbilical hernia, single umbilical artery, bilateral clenched hand, thymus hypoplasia, syndactyly, absent gallbladder	Postnatal exitus
7	47, X*		ARSA, eosophageal atresia, polyhydramnios, pouch sign	Postnatal exitus
8	47, X*, +18		ARSA, omphalocele, clenched hand, rocker-bottom foot, choroid plexus cyst	TOP
9	46, X*	22q11.2 deletion	ARSA, double outlet right ventricle	
10	46, X*	22q11.2 deletion	ARSA, interrupted aortic arch, perimembranous ventricular septal defect	TOP
11	46, X*	22q11.2 deletion	ARSA, thymus hypoplasia, mitral valve dysplasia, interrupted aortic arch, severe tricuspid valve regurgitation	Postnatal exitus
12	46, X*	11q24.2q25 deletion	ARSA, pleural effusion, ventricular septal defect	
13	46, X*		ARSA, diaphragmatic hernia, bilateral cleft lip and palate, inlet ventricular septal defect	TOP
14	46,X*		ARSA, Transposition of the great arteries, thymus hypoplasia	
15	46, X*	Normal	ARSA, hypoplastic left heart, aortic arch hypoplasia, persistent left superior vena cava, cystic hygroma	Postnatal exitus
16	46, X*		ARSA, congenital pulmonary airway malformation	
17	46,X*		ARSA, ileal atresia, gastrointestinal duplication cyst	
18	46, X*		ARSA, crossed-fussed renal ectopia, choroid plexus cyst	
19	46, X*		ARSA, ventricular septal defect, hyperechogenic cardiac focus, hyperechogenic bowel	
20	46, X*		ARSA, polyhydramnios, hypospadias	
21	46, X*		ARSA(isolated)	
22	46, X*		ARSA(isolated)	
23	46, X*		ARSA(isolated)	

Abbreviations: CNV, copy number variant; ARSA, aberrant right subclavian artery; TOP, termination of pregnancy; SNP, single nucleotide polymorphism; NCK, Normal Constitutional Karyotype.

deletion was reported for 1 (1/5) case and normal array was reported normal for 1 (1/5) case (Table 2).

In the isolated ARSA group, 3 pregnant women performed prenatal invasive testing and no chromosomal abnormality was detected (Table 2).

In the non-isolated case group, 12 pregnant women did not have prenatal diagnosis tests. No chromosomal anomaly was found in any of these 12 cases in postnatal evaluation.

Using SNP array and karyotype analysis in fetuses with ARSA, the total chromosomal anomaly detection rate was found 25.5% (12/47) as observed (Table 3).

Table 3. Phenotypic characteristics of 47 fetuses with ARSA

	Number of fetuses	Number of pathogenic CNV and/or SNP array
Fetuses with isolated ARSA	15	0(0 %)
Fetuses with non-isolated ARSA	32	12(37,5 %)
Total	47	12(25,5 %)

Abbreviations: ARSA, aberrant right subclavian artery; CNV, copy number variant; SNP, single nucleotide polymorphism.

Discussion

With the development of ultrasound technology and the improvement in the understanding of fetal ARSA, the rate of prenatal detection is increasing day by day. In some studies, ARSA has been closely associated with chromosomal abnormalities, and trisomy 21 has been reported in these cases.[11,12] In this study, chromosomal abnormalities were detected in eight cases by karyotype analysis. However, in four cases with ARSA with additional abnormal ultrasound findings and no chromosomal abnormality detected, SNP array was used and detected microdeletion. Conventional karyotype analysis can detect chromosomal fragment abnormalities above a certain size, whereas SNP-array sequence can detect smaller and lower copy number abnormalities as well as normal copy number abnormalities.[13,14] Therefore, SNP array may provide additional benefits and be more advantageous in the etiological detection of fetuses with isolated or non-isolated ARSA.

Some researchers have reported cases of trisomy 21 in fetuses with isolated ARSA. Therefore, they suggest that ultrasound can be used as a soft marker for prenatal screening of ARSA fetal chromosomal abnormalities and prenatal chromosomal examination, even if isolated.[15,16,17] Conversely, other studies do not recommend invasive prenatal testing for fetuses with isolated ARSA unless accompanied by additional ultrasound abnormalities.[18] It has been reported in previous studies that the presence of ARSA increases the risk of trisomy 21 syndrome.[19,20] In this study, trisomy 21 syndrome was detected in seven fetuses with ARSA with additional abnormal ultrasound findings, consistent with previous studies. Four of the fetuses diagnosed with trisomy 21 died due to additional severe anomalies in the postpartum period. Three pregnant women, who were found to have ARSA and whose chromosome analysis was reported as trisomy 21, decided to terminate the pregnancy. In this study, trisomy 18 syndrome was detected in one fetus with ARSA and additional ultrasound finding such as omphalocele, clenched hand, rocker-bottom foot, choroid plexus cyst, and pregnacy was terminated in this case.

ARSA is also associated with 22q11 deletion syndrome .[21] The Di-George syndrome is a multisystemic condition that features cardiac malformations, velopharyngeal insufficiency, hypoparathyroidism with hypocalcemia, and thymic aplasia with immune deficiency .[22,23] Three fetuses with ARSA were also diagnosed with 22q11.2 in this study. There were additional fetal cardiac anomalies in these cases. One pregnant decided to terminate, and one of the fetuses died after delivery. The other case with a diagnosis of 22q11.2 and a double outlet right ventricle additional cardiac anomaly continues to be followed up by pediatrics and was operated by cardiovascular surgery after delivery.

11q deletion, also known as Jacobsen syndrome, is a disorder of developmental delay, growth retardation, thrombocytopenia, dysmorphic features, cardiac abnormalities, and other congenital anomalies.[24] In our study, 11q24.2q25 deletion was detected with SNP array in one case with ARSA, pleural effusion, and ventricular septal defect. Prognosis and genetic counseling were given to the patient in the prenatal period and the patient decided to continue the pregnancy. The follow-up continues in the postnatal period.

Non-invasive prenatal screening tests with a high accuracy rate for chromosomal abnormalities can be offered as an alternative for patients with abnormal ultrasound findings and who do not want to perform an invasive test.[25] Non-invasive prenatal screening test was performed in 5 of 12 cases in the non-isolated group, and all of the results were reported as low risk.

One study reported that ARSA may be the only ultrasound finding in trisomy 21 as well as Di-George and Turner syndrome. Therefore, it was emphasized that ARSA screening should be a part of fetal anatomical evaluation, and standard karyotyping and FISH analysis should be recommended in patients even with isolated ARSA.[26] In our study, in isolated group, four patients who did not want to perform invasive test had non-invasive prenatal screening test and the results were reported as low risk. Similarly, no abnormal chromosomal anomaly was found in the postnatal evaluations of isolated patients.

Our study also has some limitations. The relatively low number of cases can be considered as the main limitation. Mutations in a single gene can also be the cause underlying ARSA. Therefore, in the future, the methodology can be improved by adding whole-exome sequencing analysis with multicenter high-case groups.

Conclusion

ARSA is a common soft ultrasound marker. Fetuses with isolated ARSA have a low probability of being detected with pathogenic chromosomal karyotype. Conversely, when ARSA is non-isolated and observed with other ultrasound abnormalities, the risk of pathogenic chromosomal karyotype analysis is increased remarkably. It should be informed that the possibility of chromosomal anomaly is low in isolated ARSA cases, there may be an abnormal analysis result, it is an ultrasonic soft marker, and an invasive test can be performed if desired. In these cases, prenatal genetic counseling and SNP array should be recommended to better assess fetal prognosis.

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RESEARCH ARTICLE

Comparison of the Prophylactic Use of Iron Polymaltose Complex and Ferrous Sulfate Iron Preparations in Terms of Efficacy and Side Effect Profile in Pregnant Women

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Abstract

Introduction: Pregnancy is a physiological process in which the need for iron increases. We aimed to compare the effectiveness and side effects of different oral iron supplements on pregnant women. **Methods:** 100 pregnant women between the ages of 18-45 who used Fe+2 (ferrous sulfate) valent iron supplementation during their pregnancy were included in the study as group 1. 100 pregnant women in the same age range who used Fe+3 (iron polymaltose complex) valent iron supplementation during their pregnancy were determined as group 2. Response to anemia treatment was evaluated with the results of laboratory parameters (Hgb, Hct). The side effects of the preparations used in oral iron replacement were questioned retrospectively with a questionnaire applied to the patients. **Results:** 16 of 100 patients (16%) had side effects with oral iron polymaltose complex supplementation. 43 of 100 patients (43%) had side effects with oral ferrous sulfate supplementation. The overall side effect was higher in those taking oral ferrous sulfate supplementation ($p<0.001$). Hb and Hct values measured at 3-month periods were found to be similar between the groups ($p>0.05$). The most common side effect was nausea and vomiting with 12%. **Conclusion:** Both oral ferrous sulfate and iron polymaltose complex supplementation have similar effects on hemoglobin and hematocrit levels in pregnant women without iron deficiency anemia. However, oral ferrous sulfate supplementation causes more side effects compared to iron polymaltose complex.

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Introduction

Physiological changes in pregnancy can cause difficulties in the diagnosis of hematological diseases. While the plasma volume increases by approximately 40-50% in singleton pregnancies, the amount of erythrocytes increases by approximately 15-25%, so the need for iron increases during pregnancy. Anemia in pregnancy can be defined as hemoglobin levels below 11 g/dL in the first trimester; 10.5 g/dL in the second trimester; and 11 g/dL in the third trimester.[1] Iron supplementation is commonly recommended during pregnancy to prevent and treat iron deficiency anemia, a condition that can occur due to increased demands for iron during pregnancy. Pregnant women need approximately 27-30 milligrams (mg) of iron per day, compared to 18 mg per day for non-pregnant women.[2] Iron deficiency anemia in pregnancy has been associated with increased risks such as preterm birth, low birth weight, postpartum hemorrhage and perinatal mortality. Iron deficiency anemia should be treated with anti-anaemic iron supplements in addition to prenatal vitamins.[3]

However, iron supplements can cause side effects such as metallic taste, gastric irritation, diarrhea, constipation, nausea, vomiting, or stomach discomfort.[4] Patients may also be bothered by itching and by black/green or tarry stools that stain clothing or cause anxiety about bleeding. Taking the supplement with food or using a slow-release formulation may help reduce these side effects. In a systematic review, gastrointestinal adverse effects were seen with all oral formulations but extended-release ferrous sulfate with mucoproteins appeared to be the best tolerated.[5] It's important to note that not everyone will experience side effects from iron supplementation, and the benefits often outweigh the risks when iron deficiency anemia is present. In this study, we aimed to compare the use of different oral iron supplements in pregnant women in terms of efficacy and side-effect profile.

Material and Methods

This study was designed as a retrospective observational cohort study. 100 pregnant women between the ages of 18-45 who used Fe+2 (ferrous sulfate) valent iron during their pregnancy were accepted as group 1. 100 pregnant women in the same age range who used Fe+3 (iron polymaltose complex) valent iron during their pregnancy were determined as group 2. Pregnant women who were followed up in Ankara City Hospital's perinatology outpatient clinic regularly from the first trimester were included in the study. The questionnaire was applied to pregnant women between 32-40 weeks of gestation. Pregnant women with iron deficiency anemia, multiple pregnancies, and pregnant women with systemic or pregnancy related diseases were excluded from the study. Demographic characteristics and medical and obstetric histories of the pregnant women were reviewed and noted from the hospital records. The hemoglobin (Hb) and hematocrit (Hct) parameters of the patients, which were measured at 3-month intervals, were compared. Response to anemia treatment was evaluated with the results of laboratory parameters (Hgb, Hct). The side effects of the preparations used in oral iron replacement were questioned retrospectively with a questionnaire applied to the patients. The study protocol was performed in line with the Declaration of Helsinki. This study was approved by the Ankara City Hospital institutional review board (12.07.23/ E2-23-4487).

Statistical analysis

IBM SPSS version 25 software (Armonk, NY) was used for statistical analyses. The variables were investigated using the Kolmogorov-Simirnov test to determine whether or not they are normally distributed. Student's T-test was used to compare two normally distributed independent variables. Descriptive analyses were presented using mean±SD for the normally distributed variables. The chi-square test was used for categorical variables and values were presented as N (%). A p-value of less than 0.05 was considered to show statistically significant results.

Results

A comparison of demographic and clinical characteristics of pregnant women using iron polymaltose complex and ferrous sulfate iron supplements were shown in Table 1. Maternal age, gravida, parity, BMI, and gestational age at birth were similar between the groups ($p>0.05$). It was observed that the gestational week at which supplementation was started was earlier in pregnant women using ferrous sulfate iron preparations ($p=0.005$). The mean duration of oral iron preparation use was 18.1±8.4 in the iron polymaltose complex group and 21.5±8.5 in the ferrous sulfate group. The usage time was statistically longer in the ferrous sulfate group ($p=0.005$).

Table 1. Comparison of demographic and clinical characteristics of pregnant women using Fe+3 and Fe+2 valence iron supplements

Variables	Fe+3 (n=100)	Fe+2 (n=100)	p
Maternal age (year)	28.3±6.1	27.8±5.3	0.58
BMI (kg/m^2)	28.4±4.3	28.2±3.5	0.71
Gravida	2.1±1.2	2±1.2	0.65
Parity	0.8±0.9	0.7±0.9	0.88
Abortion	0.3±0.6	0.3±0.7	0.34
Gestational age (week)	36.3±2.1	36.7±2.1	0.21
duration of iron supplement use (week)	18.5±7.8	15.2±8.2	0.005
Usage time (week)	18.1±8.4	21.5±8.5	0.005

BMI: Body mass index.
Student's T-test; Results were presented as mean±SD. p<0.05 values were presented in bold

A comparison of the side effect profile in pregnant women using iron polymaltose complex and ferrous sulfate iron supplements was shown in Table 2. 16 of 100 patients (16%) had side effects with oral iron polymaltose complex. 43 of 100 patients (43%) had side effects with oral ferrous sulfate. The overall side effect was higher in those taking oral ferrous sulfate (p<0.001). The most common side effect was nausea-vomiting at 12%, and the second most common side effect was constipation at 10%.

Table 2: Comparison of the side effect profile in pregnant women using Fe+3 and Fe+2 valent iron supplements

Variables (n, %)	Fe+3 (n=100)	Fe+2 (n=100)	p
Presence of side effects	16 (16%)	43 (43%)	**<0.001**
Nausea-vomiting	4 (4%)	12 (12%)	
Stomach discomfort	3 (3%)	7 (7%)	
Diarrhea	0 (0%)	4 (4%)	
Bloating	0 (0%)	2 (2%)	**0.005**
Color change in stool	3 (3%)	6 (6%)	
Constipation	6 (6%)	10 (10%)	
Metallic taste	0 (0%)	2 (2%)	

Chi-Square Test; results were presented as number (%). p<0.05 values were presented in bold

First, second, and third trimester Hb and Hct values of pregnant women using iron polymaltose complex and ferrous sulfate iron supplements were compared in Table 3. Hb and Hct values measured at 3-month periods were found to be similar between the groups. No statistically significant difference was detected (p>0.05).

Table 3: First, second, and third trimester Hb and Hct values of pregnant women using Fe+3 and Fe+2 valence iron supplements

Variables	Fe+3 (n=100)	Fe+2 (n=100)	P
First trimester Hb (g/dl)	12.8±1.2	12.6±1.3	0.33
First trimester Hct (%)	38.3±3.8	37.9±3.5	0.60
Second trimester Hb (g/dl)	11.5±1.1	11.4±1.1	0.35
Second trimester Hct (%)	35.2±2.8	34.7±3.1	0.17
Third trimester Hb (g/dl)	11.4±1.1	11.7±1.2	0.31
Third trimester Hct (%)	34.8±3.1	35.5±3.5	0.21

Hb: Hemoglobin, Hct: Hematocrit
Student's T-test; results were presented as mean±SD

Discussion

Iron is an essential mineral that plays a vital role in the production of hemoglobin, the protein in red blood cells that carries oxygen throughout the body. The iron requirements increase during pregnancy to support the growing fetus, placenta, and maternal blood volume expansion. In our study, we found that the type of different oral iron supplements did not affect the gestational age at birth. Side effects were more common in those using oral ferrous sulfate supplements. These side effects included nausea, vomiting, stomach discomfort, diarrhea, bloating, gastric irritation, constipation, and metallic taste. These findings were consistent with the literature.[4] None of the pregnant women in the study had anemia in the first trimester. First trimester, second trimester, and third trimester Hb Hct values did not change according to the oral iron supplement used.

In a retrospective cohort study from China, it was found that compared with no anemia, anemia severity during pregnancy was associated with increased risks of placental abruption, preterm birth, severe postpartum hemorrhage, and fetal malformation.[6] Conversely, a review noted that supplementation of iron, folic acid, or both to pregnant women, either anemic or not, did not increase the birth weight or gestational week.[3] We did not find any difference at gestational week at birth either. Another study stated that the prevalence of anemia overall and by pregnancy trimester was higher among African American (Black) women than among other ethnic groups. The prevalence of anemia was higher among women evaluated in the third trimester of pregnancy than among those evaluated in the first or second trimester.[7]

There are some studies in the literature comparing the efficacy and tolerability of oral Fe+2 (ferrous sulfate) and Fe+3 (polymaltose complex) supplementation in pregnant women. The Common view is that both oral supplement types were equally effective, but fewer side effects were seen with the polymaltose complex.[4,8,9] Similar results were found in some studies among non-pregnant adult groups, and it was stated that the frequency of gastrointestinal side effe-

cts of the ferrous product was significantly higher, but both supplements were well tolerated.[10] Numerous clinical trials in men, women, children, and infants have shown a lower rate of treatment interruption with polymaltose complex than with ferrous sulfate.[11] It was also shown that iron polymaltose complex improved the cognitive function, and scholastic performance of adolescents with and without iron deficiency and anemia.[12] However, among children who received ferrous sulfate therapy for iron deficiency anemia, higher hemoglobin levels of ferrous sulfate were found to have fewer side effects compared to children who received iron polymaltose complex.[13] In laboratory studies on rats and in vitro studies, it has been shown that the iron polymaltose complex does not interact with commonly used drugs such as acetylsalicylic acid, tetracycline hydrochloride, calcium phosphate, methyl-L-dopa, magnesium hydrochloride, and none of them has a significant effect on iron absorption.[14,15] The small number of cases was the major limitation of our study. In addition, iron deficiency anemia was not observed in any of the pregnant women in both groups at the beginning of iron supplementation. We performed this study on pregnant women without iron deficiency anemia who received prophylactic iron supplementation.

Conclusion

In conclusion, both oral ferrous sulfate and iron polymaltose complex supplementation in pregnant women have similar effects on hemoglobin and hematocrit levels in pregnant women without iron deficiency anemia. However, oral ferrous sulfate supplementation causes more side effects compared to iron polymaltose complex. Our findings were consistent with the literature. Further studies are needed to obtain definitive results.

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None

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RESEARCH ARTICLE

Management of Non-Surgical Traumatic Facial Nerve Injuries

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Abstract

Introductıon: Traumatic facial nerve injuries present a unique challenge to clinicians and surgeons because of the intricate facial nerve anatomy and profound impact on the psychological well-being and social interactions of patients. In this study, we aimed to shed light on the multifaceted nature of non-iatrogenic traumatic facial nerve injuries through an in-depth analysis of 12 distinctive cases. **Methods:** Between March 2019 and June 2022, at Ankara City Hospital and Akdeniz University Hospital, we conducted a retrospective analysis of 12 patients who presented with traumatic facial nerve injuries without surgery-related complications. To better understand the particularities of traumatic injuries to the facial nerve outside the context of surgical interventions, all cases selected for this study were of nonsurgical origin. **Results:** Twelve patients (eight males and four females) were included in the study. The average age of the patients was 29 years (range, 5–53 years). The causes of injury varied from dog bites in one patient, work-related injuries with a jigsaw in one patient, traffic accidents in two patients, sharp penetrating injuries in four patients, and temporal bone trauma in four patients. Five patients underwent a direct nerve repair. Three patients had nerve grafting. Three patients underwent reconstruction using a free functional gracilis flap. One patient underwent masseter nerve transfer. Considering the diverse treatment modalities applied and the subsequent outcomes observed, an algorithm was formulated. **Conclusion:** By sharing these experiences, we aspire to contribute a nuanced perspective to the existing body of knowledge on traumatic facial nerve injuries, further supporting clinical decision-making in such rare and challenging scenarios.

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Introduction

The facial nerve, or seventh cranial nerve, is one of the most intricate and clinically significant structures in human anatomy.[1] The facial nerve serves primarily for motor innervation of the facial muscles and transmission of taste sensations. Any injury or anomaly involving this nerve can affect facial movement, expression, and overall quality of life.[2] Traumatic facial nerve injuries present a unique challenge to clinicians and surgeons because of the intricate facial nerve anatomy and profound impact on patients' psychological well-being and social interactions. The etiology of traumatic facial nerve injuries varies from blunt and penetrating trauma to iatrogenic injuries during surgical procedures.[3] Although iatrogenic facial nerve injuries, owing primarily to surgical interventions, have been well documented, the literature offers limited insights into non-iatrogenic traumatic facial nerve injuries. Such injuries, which are less prevalent in clinical scenarios, often present unique diagnostic and therapeutic challenges owing to their distinct etiologies and presentations. Regardless of the cause, the primary goal of treatment is to restore facial symmetry and function. The spectrum of management approaches for these injuries has expanded significantly over the past few decades thanks to advances in surgical techniques, microsurgery, and an improved understanding of nerve physiology.[4] Direct repair, which involves coaptation of nerve ends, has been a cornerstone treatment approach for many years. However, when direct repair is not feasible or in cases with a significant loss of nerve tissue, nerve grafts may serve as a viable solution.[5] More recently, innovative approaches, such as using a free functional gracilis flap or performing masseteric nerve transfer, have expanded the therapeutic horizons for cases where traditional methods might not suffice or have previously failed.[6,7] In this study, we aimed to shed light on the multifaceted nature of non-iatrogenic traumatic facial nerve injuries through an in-depth analysis of 12 distinctive cases.

Material and Methods

We conducted a retrospective analysis of 12 patients who presented with traumatic facial nerve injuries without surgery between March 2019 and June 2022 at Ankara City Hospital and Akdeniz University Hospital. The inclusion criteria were as follows: all traumatic facial paralysis cases selected for this study were exclusively of non-surgical origin; the patients were children or adults; the patients were men or women; and the first intervention was for facial nerve damage. Patients for whom there was a switch to another surgical or result evaluation method were excluded.

This study was approved by the local ethics committee (Approval Number: KAEK-597). Furthermore, the research adhered to the guidelines set forth by the Declaration of Helsinki, ensuring that ethical considerations and patient rights were of paramount importance.

To evaluate facial nerve function pre-and postoperatively, we used the House–Brackmann (HB) scoring system. The HB scoring system, a globally recognized grading system, was used to quantify the degree of facial palsy in the patients, facilitating objective comparisons and assessments of therapeutic outcomes.[8]

Patient data, including demographic details, etiology of injury, time to presentation, HB scores before and after the intervention, and specifics of the surgical procedure, were collected from medical records. All patients were treated by a physiotherapist after the surgical procedure, and patient compliance with physiotherapy was not evaluated.

Results

Twelve patients (eight males and four females) were included in the study. The average age of the patients was 29 years (range, 5–53 years). The mean follow-up period was 15 months. The causes of injury varied from dog bites in one patient, work-related injuries with a jigsaw in one patient, traffic accidents in two patients, sharp penetrating injuries in four patients, and temporal bone trauma in four patients (Table 1). One patient (Case 4) did not undergo any facial nerve decompression surgery because it was thought that there will be no benefit. And other 3 patients with temporal bone fracture had undergone decompression surgery but did not benefit from.

Facial nerve injuries were more common on the right side (seven patients, 58%) than on the left side (five patients, 42%). A detailed breakdown of the injuries, times to presentation, HB scores both before and after the intervention, and specifics of the surgical procedures are presented in Table 1.

Our surgical interventions varied based on the specifics of each case. Five patients underwent direct nerve repair; three patients received nerve grafting; three had the facial nerve reconstructed using the free functional gracilis flap; and one underwent mas-

seteric nerve transfer. Facial nerve healing was not followed by EMG. Recovery was recovery was followed clinically with Tinel test at every consultation.

Acute injuries were treated with direct repair or nerve grafting, as appropriate. Buccal branch masseter nerve transfer was specifically performed in one patient who did not exhibit facial nerve recovery during follow-up (Figure 1). Patients with late-onset facial nerve trauma underwent reconstruction using a functional gracilis muscle flap (Figure 2). In these cases, nerve anastomosis was performed between the masseter and obturator nerves.

Most patients showed improved HB scores after treatment, with the only exceptions being the patients who underwent nerve graft repair. Furthermore, two patients (Patients 3 and 12) had grade-1 HB scores. A common characteristic of these patients was the repair time, which was within 24 h after injury.

Table 1. Patients' characteristics

Case	Sex	Age (years)	Trauma Type	Affected Branches	Time from Injury to Presentation	Follow-up (Months)	House-Brackmann score before treatment	Reconstruction Method	House-Brackmann score after treatment
1	F	5	Dog-bite injury	Fascial Nerve Trunk	Within 24 Hours	14	6	Primary repair	2
2	M	25	Knife	Fascial Nerve Trunk	72 Hours	12	6	Repair with nerve graft (sural nerve)	4
3	M	45	Work-related, Jigsaw	ZB, FB	Within 24 Hours	15	4	Primary repair	1
4	F	43	Traffic accident	Temporal Bone Fracture	3 months	18	6	Masseteric nerve transfer to buccal branch	3
5	F	53	Glass	ZB, FB, BB, MMB	48 Hours	12	6	Primary repair	2
6	M	37	Blunt trauma to head	Temporal Bone Fracture	10 years	17	5	Functional gracilis muscle transfer	2
7	M	10	Blunt trauma to head	Temporal Bone Fracture	8 years	18	5	Functional gracilis muscle transfer	2
8	M	29	Blunt trauma to head	Temporal Bone Fracture	2 years	16	6	Functional gracilis muscle transfer	2
9	F	32	Glass	Fascial Nerve Trunk	72 hours	14	6	Repair with nerve graft (sural nerve)	4
10	M	18	Knife	Fascial nerve trunk	48 hours	14	6	Repair with nerve graft (sural nerve)	3
11	M	25	Traffic accident	ZB, BB	Within 24 hours	12	5	Primary repair	2
12	M	31	Glass	FB,ZB	Within 24 hours	14	4	Primary repair	1

ZB: Zygomatic branch, FB: Frontal branch, BB: Buccal branch, MMB: Marginal mandibular branch

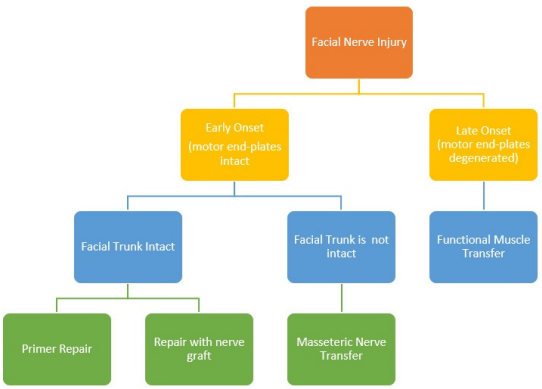

Figure 1: Treatment algorithm of non-surgical traumatic facial nerve injuries

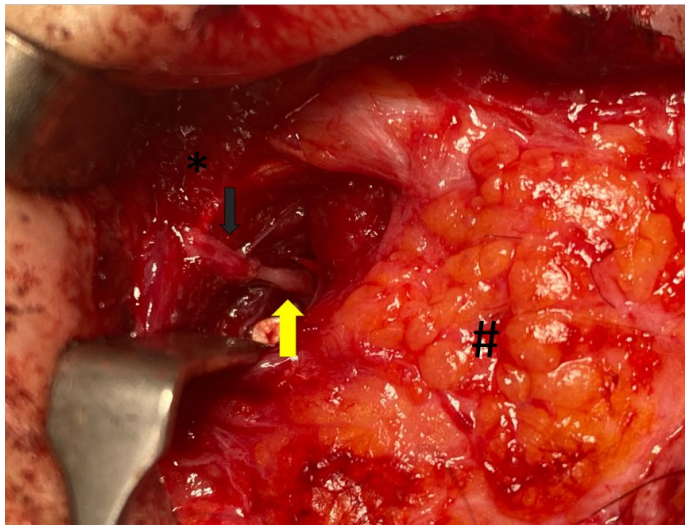

Figure 2. Intraoperative view of masseteric nerve transfer of Case 4. *: Massater muscle, #: Parotis gland, Black arrow: Masseteric nerve, Yellow arrow: Buccal Nerve

Based on our observations and surgical outcomes, we formulated an algorithm to address traumatic facial nerve injuries, as shown in Figure 3. This algorithm encapsulates the decision-making process and serves as a guide for potential therapeutic interventions in traumatic facial nerve injuries.

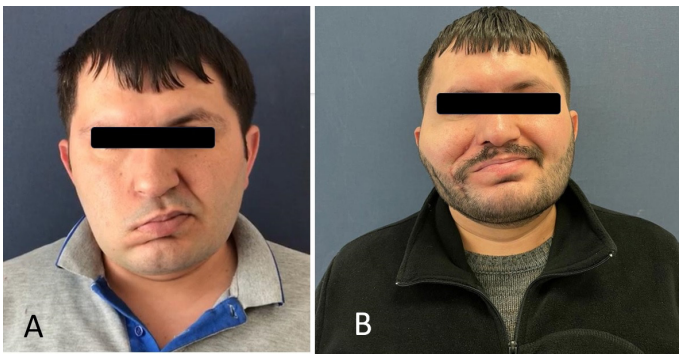

Figure 3: Case 6 a) Preoperative photo of the Case 6. b) 13 months After functional gracilis muscle transfer, gracilis muscle bulk can be seen at cheek level.

Discussion

Management of traumatic facial nerve injuries requires surgical expertise, timely interventions, and structured postoperative care. In conjunction with previous studies, this study seeks to provide a

comprehensive approach for optimizing the outcomes of such injuries. Moreover, this study focused on traumatic facial nerve injuries due to non-surgical causes to fill an existing gap in the current literature.

The HB scoring system employed in our study remains the main approach for assessing facial nerve function. Its widespread acceptance stems from its objectivity and granularity, which allow standardized comparisons across cases. Our findings indicated a significant improvement in HB scores across most cases after intervention, testifying to the efficacy of our approach. These findings are also supported by previous studies. A study of surgical timing and outcomes by Kim et al. stressed the utility of the HB scoring system as a reliable indicator of functional recovery.[9]

The surgical choice between primary repair, nerve grafting, nerve transfer, and muscle transfer approaches is pivotal. Frijters and Fliss highlighted the consistent outcomes associated with primary repair and the occasional unpredictability associated with nerve grafting.[10,11] This inconsistency was notable in our case series; thus, nerve grafting did not yield the desired outcomes in two out of the three cases. The underlying reasons for this variability may lie within individual variations in nerve regeneration, surgical techniques, or graft quality, warranting further exploration. As expected, we obtained the best scores for the primary repairs in our study.

Surgical intervention is the first step towards patient recovery, with post-facial nerve repair physiotherapy playing a crucial role in functional restoration. Physical rehabilitation aids in preventing muscle atrophy, promoting nerve regeneration, and retraining the facial muscles.[12] The role of physiotherapy has become even more crucial in cases involving muscle transfers or nerve grafts, where neural-muscular dynamics are significantly altered.[12] The emphasis on early and structured physiotherapy may partly explain the notable improvements observed in our patient cohort. Although we did not evaluate the effect of post-surgical physiotherapy in our study, this is an important part of the treatment, regardless of whether primary repair or muscle transfer is performed.

Chronic presentation adds another layer of complexity. As elucidated by Erkan and Carre, the surgical decision between muscle and nerve transfers depends on the time elapsed since injury.[5,12] Our algorithm provides a structured approach to these decisions, ensuring that interventions are timely and evidence-based.

In conclusion, the management of traumatic facial nerve injuries requires a holistic approach, beginning with timely surgical intervention guided by anatomical precision, followed by dedicated postoperative physiotherapy. The HB scoring system is a valuable tool for ongoing assessment and monitoring, and allows clinicians to tailor interventions and rehabilitation according to individual patient needs. With the growing body of evidence, it is imperative that clinicians remain abreast of the latest techniques and findings, ensuring that patients receive the best possible care at every stage of their recovery. Building on previous studies, our study helps provide clinicians with a comprehensive guide for managing these injuries and ensuring improved facial function and patient satisfaction.

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RESEARCH ARTICLE

Investigating the Relationship of Vitamin D Deficiency and Certain Biochemical Parameters with Depression

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Abstract

Introductıon: Depression is the most common psychiatric disorder in the general population and is the most common mental health condition in primary care patients. Although theories involving biological, psychological, and environmental factors have been put forth, the underlying pathophysiology of depression is unknown, as several different mechanisms are likely involved. Identification of vitamin D receptors in brain regions active in depression has strengthened the link between vitamin D and depression. The aim of this study was to examine the relationship of depression with vitamin D and certain biochemical parameters. **Methods:** Patients who were admitted to Şanlıurfa Mehmet Akif İnan Training and Research Hospital Internal Medicine outpatient clinic who had no chronic diseases and whose vitamin D, ferritin, hemoglobin (Hb), thyroid stimulant hormone (Tsh), free thyroxine (T4), folate, magnesium and B12 levels were recorded were included in the study. Beck's Depression Inventory was presented to the patients to examine the relationship of depression with the selected parameters. **Results:** A total of 352 cases were included in the study. Of the cases, 246 (69.9%) were female and 106 (30.1%) were male. There was no significant correlation between Beck's Depression Inventory scores and magnesium, hemoglobin, ferritin, B12, Tsh and T4 levels ($p>0.05$). A significant correlation was found only between folate levels and Beck's Depression Inventory scores ($p=0.046$). There was not a significant correlation between vitamin D levels and Beck's Depression Inventory scores ($p=0.727$), although a weak negative correlation was discovered between them ($r= -0.019$). There was no significant correlation between vitamin D levels and depression severity ($p=0.650$). None of the patients who had normal vitamin D levels were found to have severe depression. **Conclusion:** Depression is a common psychiatric disease and its pathophysiology has not been fully elucidated. Further studies are need to better understand the relationship between biochemical parameters and depression. The evidence-based results of these studies should be used to prevent and treat depression, which is an important health problem.

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Introduction

Depression is the most widespread psychiatric disorder in the general population and is also the most common mental health condition in primary care patients.[1] It is characterized by a despondent mood or loss of interest or pleasure in almost all activities for a period of at least two weeks. Symptoms of depression include changes in sleep patterns, appetite and psychomotor function, irritability, feelings of worthlessness, guilt and hopelessness, suicidal thoughts or attempts, and decreased energy. Major depressive disorder, which is more common in females (10-25%) than in males (5-12%), significantly affects everyday activities and social relationships. The average age of onset of depression is the mid-twenties, and in 50-60% of those who experience a single depressive episode, depression recurs and is often associated with anxiety.[2]

Although theories involving biological, psychological, and environmental factors have been developed, the underlying pathophysiology of depression is unknown and several different mechanisms are reportedly involved. Vitamin D, a neurosteroid hormone, has been shown to affect the pathology of depression. Receptors for vitamin D are found in neurons and glia in many regions of the brain, including the cingulate cortex and hippocampus, which are involved in the pathophysiology of depression.[3] Vitamin D plays a part in numerous brain processes such as neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity, and brain development, which makes it biologically plausible that this vitamin may be associated with depression and that its supplementation may factor into the treatment of depression.[4]

Recent studies have reported that vitamin D is significant in the prevention and treatment of many chronic diseases.[5] Identification of vitamin D receptors in brain regions involved in depression strengthened the link between vitamin D and depression. Prior human and animal studies showed that vitamin D receptors and the 1-α-hydroxylase enzyme are found in the brain and vitamin D has a role in central nervous system functions.[6,7] The aim of this study was to examine the relationship of depression with vitamin D and a few specific biochemical parameters.

Material and Methods

Ethics approval was obtained from the institutional review board prior to initiation of the study. Those included in the study were patients who were admitted to Şanlıurfa Mehmet Akif İnan Training and Research Hospital Internal Medicine outpatient clinic who had no chronic diseases and whose vitamin D, ferritin, hemoglobin (Hb), thyroid cytimulan hormone (Tsh), free thyroxine (T4), folate, magnesium and B12 levels were recorded. Beck's Depression Inventory (BDI) was given to the patients to examine the relationship of depression with the selected parameters. BDI was developed by Beck et al. in 1961 to measure behavioral findings of depression in adolescents and adults.[8] In 1978, the whole scale was revised, duplications of statements defining severity were removed and the questions were reorganized to examine the status of the patients during the prior week, including the day they on which they completed the test. Regarding severity, scores are interpreted as 0-9 = Minimal, 10-16 = Mild, 17-29 = Moderate, and 30-63 = Severe.[9] This scale is open-access. Patients with active malignancy, liver failure, renal failure, chronic diseases and those under 18 years of age were excluded from the study.

Statistical Analysis

Descriptive statistics were used to explain the data of the study. Quantitative variables were described using means and standard deviation (x ± SD) and qualitative variables were described using numbers (n) and percentages (%). Differences between groups regarding quantitative variables were evaluated with Independent Sample T Test or One-Way Analysis of Variance (ANOVA). Differences between groups regarding qualitative variables were analyzed with the Chi-Square Test. Pearson's Correlation Analysis was used to examine the relationships between quantitative variables. A significance level of $p<0.05$ was considered statistically significant. Statistical software was used for calculations (IBM SPSS Statistics 22, SPSS inc., an IBM Co., Somers, NY)

Results

A total of 352 Cases were included in the study. Of the cases, 246 (69.9%) were female and 106 (30.1%) were male. The ages of the patients ranged between 18 and 74 years, with a mean age of 33.32±11.86 years (Table 2). Of these patients, 212 (60.2%) were

between the ages of 18-34 years, 136 (38.6%) were between the ages of 35-64 years, and 4 (1.1%) were over the age of 65 years. There were 115 (32.7%) primary school graduates, 18 (5.1%) secondary school graduates, 97 (27.6%) high school graduates, and 102 (29%) with a bachelor's or master's degrees. While 143 (40.6%) of the patients were employed, 209 (59.4%) were not. 64 (18.2%) of the patients were smokers and 288 (81.8%) were non-smokers. Only 2.8% of the cases (n=10) consumed alcohol (Table 1).

Table 1: Distribution of Qualitative Characteristics (n=352)

		n	%
Age	18-34	212	60.2
	35-64	136	38.6
	65+	4	1.1
Gender	Female	246	69.9
	Male	106	30.1
Education	No	20	5.7
	Primary school	115	32.7
	Secondary school	18	5.1
	High school	97	27.6
	Bachelor or Master	102	29.0
Employment	Employed	143	40.6
	Unemployed	209	59.4
Smoking	No	288	81.8
	Yes	64	18.2
Alcohol Use	No	342	97.20
	Yes	10	2.80
BDI	Minimal Depression	76	21.60
	Mild Depression	92	26.10
	Moderate Depression	151	42.90
	Severe Depression	33	9.40
Vitamin D	Severe Deficiency	304	86.40
	Deficiency	39	11.10
	Normal	9	2.60

Table 2. Distribution of Quantitative Characteristics (n=352)

	Mean	Standard Deviation	Median	Minimum	Maximum
Age	33.32	11.86	31.00	18.00	74.00
BDI	17.68	8.92	17.00	0.00	49.00
Mg	2.01	0.14	2.01	1.20	2.47
Hb	13.19	2.14	13.00	7.10	18.00
Ferritin	49.58	66.69	25.00	1.57	442.90
Vitamin D (Ng/ml)	12.05	7.05	10.12	0.85	63.00
B12	316.46	125.49	292.00	50.00	890.30
Folate	6.57	4.36	5.60	1.31	58.00
Tsh	2.23	1.72	1.78	0.01	16.13
T4	15.23	2.76	15.00	6.40	42.63

Patients' BDI scores varied between 0 and 49. The mean BDI score was 17.68±8.92 (Table 2). Of the patients, 76 (21.6%) had minimal depression, 92 (26.1%) had mild depression, 151 (42.9%) had moderate depression, and 33 (9.4%) had severe depression (Table 1).

Vitamin D levels of the patients ranged between 0.85 ng/ml and 63 ng/ml with a mean of 12.05±7.05 ng/ml (Table 2). A severe vitamin D deficiency was found in 304 of the patients (86.4%), while 39 (11.1%) had less severe vitamin D deficiency, and 9 (2.6%) had normal vitamin D levels (Table 1).

Magnesium values of the patients ranged between 1.2 and 2.47 mg/dl with a mean value of 2.01±0.14 mg/dl. Their hemoglobin (Hg) values ranged between 7.1 and 18 g/dl and the mean value was 13.19±2.14 g/dl. Ferritin levels ranged between 1.57 and 442.9 ng/ml with a mean value of 49.58±66.69 ng/ml. Vitamin B12 levels varied between 50 and 890.3 pg/ml, with a mean of 316.46±125.49 pg/ml. Folic acid levels of the patients had a range between 1.31 and 58 ng/ml with the mean value being 6.57±4.36 ng/ml. Tsh levels varied between 0.01 and 16.13mIU/L with a mean value of 2.23±1.72mIU/L. Free T4 levels ranged between 6.4 and 42.63 mIU/L with a mean value of 15.23±2.76 mIU/L (Table 2).

No significant correlation was found between BDI scores and age, gender, educational status, employment status, smoking and alcohol use (p=0.880, p=0.762, p=0.380, p=0.397, p=0.105, p=0.337, respectively).

There was also no significant correlation between BDI scores and magnesium, hemoglobin, ferritin, B12, Tsh, or Free T4 levels (p=0.923, p=0.740, p=0.313, p=0.818, p=0.109, p=0.810, respectively). BDI scores only had a significant correlation with folate levels (p=0.046). A negative correlation was found between BDI scores and ferritin, folate and Tsh levels (r=-0.054, r=-0.106, r=-0.086, respectively). There was a positive correlation between BDI scores and magnesium, hemoglobin, B12 and free T4 levels and (r=0.005, r=0.018, r=0.012, r=0.013, respectively) (Table 3).

There was no significant correlation between vitamin D levels and BDI scores (p=0.727), although there was a weak negative correlation between them (r=-0.019). There was no significant correlation between vitamin D levels and depression severity (p=0.650). None of the patients who had normal vitamin D levels were found to have severe depression (Table 4).

Table 3. Relationship Between Quantitative Characteristics and BDI Scores (n=352)

		BDI
Mg	r	0.005
	p	0.923
Hb	r	0.018
	p	0.740
Ferritin	r	-0.054
	p	0.313
B12	r	0.012
	p	0.818
Folate	r	-0.106
	p	0.046*
Tsh	r	-0.086
	p	0.109
T4	r	0.013
	p	0.810
Vitamin D (Ng/ml)	r	-0.019
	p	0.727

r: Pearson's Correlation Coefficient
* A p value of 0.05 was considered significant.

Interpretation:
r<0.4 is considered a weak correlation.
r=0.4-0.6 is considered a moderate correlation.
r> 0.6 is considered a strong correlation.

Table 4. Relationship Between Vitamin D Levels and Depression Severity (n=352)

		Vitamin D			p
		Severe Deficiency	Deficiency	Normal	
BDI	Minimal Depression	64(84.2)	9(11.8)	3(3.9)	0.653
	Mild Depression	80(87.0)	8(8.7)	4(4.3)	
	Moderate Depression	131(86.8)	18(11.9)	2(1.3)	
	Severe Depression	29(87.9)	4(12.1)	-	

Data is presented as n (%).
p: Chi-Square Test, * A p value of 0.05 was considered significant.

No significant correlation between vitamin D levels and age was found (p=0.202). Vitamin D levels of females (mean of 11.12±7.49 ng/ml) were significantly lower than those of males (mean of 14.22±5.34 ng/ml) (p<0.001). There was no statistically significant correlation between educational status and vitamin D levels (p=0.101). Vitamin D levels of employed patients were significantly higher than those of unemployed patients (p=0.003). No statistically significant correlation was found between smoking and alcohol use and vitamin D levels (p=0.773 and p=0.137, respectively).

Discussion

Prior studies examining the relationship between vitamin D levels and depression have conflicting results. Studies have suggested that vitamin D deficiency triggers depression through different mechanisms. Saji Parel et al. argued that vitamin D deficiency may lead to depression by affecting gene expressions, some neurotransmitters and various brain functions.[10-11]

In a study by Lars Libuda et al. involving approximately 322,000 participants, no relationship was found between vitamin D levels and depression symptoms and severity.[12]

Leila Kamalzadeh et al. investigated the relationship between vitamin D deficiency and depression in 174 obese patients, and found that vitamin D deficiency was significantly more common in depressive patients (p<0.05).[13]

In Menon et al.'s review of a total of 61 articles, including 46 original articles, 13 review/meta-analysis articles and two commentaries, it was found that depressive subjects had significantly lower vitamin D levels compared to controls and those with the lowest vitamin D levels had the greatest risk of depression .[14]

The results of studies suggesting a relationship between vitamin D deficiency and depression do not answer the question of whether vitamin D deficiency is a cause or a consequence of depression. This is because introversion and decreased interest in daily activities, which are common in individuals with depression, affect time spent outdoors, and therefore, time spent under the sun. Consequently, vitamin D levels in these people naturally decrease over time.

In our study, no significant correlation between vitamin D levels and Beck's Depression Inventory scores was found (p=0.727), though a weak negative correlation was detected (r= -0.019). There was also no significant correlation between vitamin D levels and depression severity (p=0.650). In addition, none of the patients who had normal vitamin D levels were found to have severe depression.

The fact that the number of patients with normal vitamin D levels was low (n=9) is a limi-

tation of this study. In addition, lower levels of vitamin D in females may be related to the fact that females in Turkey dress more conservatively and are less exposed to the sun than males.

In the current study, a weak negative correlation was found between folate levels and BDI scores. As folate levels decreased, BDI scores increased significantly (p=0.046). This result was consistent with the results of previous studies.

Numerous studies have found associations between low folate levels and increased risk of depression,[15-16] more severe depressive symptoms,[17] increased risk of recurrence of depressive symptoms,[18] and prolonged depressive episodes.[19]

In a meta-analysis of 43 studies that included a total of 8,519 participants with depression and 27,282 participants without depression, it was found that depressive individuals had significantly lower serum folate levels compared to individuals without depression ($p < 0.001$).[20]

The results of studies on the relationship between B12 deficiency and depression are inconsistent. The results of one study suggested that vitamin B12 deficiency may play a role in the pathology of depression through its effects on the adrenergic, glutaminergic, serotonin, and dopamine systems.[21] In a 6-year study conducted with elderly patients by Elstgeest et al., no relationship was found between serum vitamin B12 levels and depression symptoms.[22] Yet another study has found no relationship between vitamin B12 levels and depression.[23]

The results of the present study also indicated no significant relationship between B12 levels and BDI scores (p=0.818).

In a study conducted with 60 depressed individuals with hypomagnesemia, a significant improvement in serum magnesium levels and depression symptoms was found in the experimental group after being given 500 mg magnesium oxide for 8 weeks .[24]

The results of another study showed a relationship between serum magnesium levels and depression symptoms, and suggested that magnesium supplementation may improve depressive symptoms in individuals with low serum magnesium levels.[25]

In our study, no statistically significant relationship was found between Mg levels and BDI scores (p=0.923). Since the extracellular concentration of magnesium ions may not reflect intracellular concentrations, none of the available assessment methods for magnesium levels are considered satisfactory.[26] This may explain the inconsistency between the results of the present study and prior research.

In a study conducted with 11,876 Japanese participants, which included 1,000 individuals with a history of depression, iron deficiency anemia was found to be associated with depression. In addition, self-reported lifetime history of iron-deficiency anemia was found to be associated with higher psychological distress ($p<0.01$).[27]

However, the results of the current study indicated no significant relationship between BDI scores and Hg and ferritin levels (p=0.740, p=0.313, respectively). The fact that our study objectively evaluated anemia diagnoses can be highlighted as a strength of this research.

In their study that included 2,142 participants, Ittermann et al. found that untreated hypothyroidism was associated with a higher BDI scores and more severe anxiety. In addition, untreated hyperthyroidism has been linked to a higher risk of major depressive disorder.[28]

In contrast, no statistically significant correlation was found between BDI scores and TSH and ST4 levels in the present study (p=0.109, p=0.810, respectively).

Conclusion

Depression is an important public health problem all over the world. Further studies are need to better understand the relationship between biochemical parameters and depression. The evidence-based results of these studies should be used among efforts to prevent and treat depression.

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RESEARCH ARTICLE

The Comparison of Intravenous Immunoglobulin and Subcutaneous Immunoglobulin Treatments in Primary Immunodeficiency Diseases

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Primary immunodeficiency diseases, subcutaneous immunoglobulin, intravenous immunoglobulin

Abstract

Introduction: Primary immunodeficiency diseases (PIDD) cause increased sensitivity against infections. The main treatment of PIDD is regular immunoglobulin (Ig) replacement therapy. IgG replacement therapy can be administered intravenously (IVIG) or subcutaneously (SCIG). SCIG and IVIG treatments are similarly effective in preventing infections in PIDD **Methods:** This retrospective study was conducted in tertiary pediatric immunology department during the 3 years. We compared the cost-effectiveness, adverse reactions, serum IgG trough levels, infection rates, antibiotic usage, infection-related hospitalization, effectiveness, safety and tolerability of SCIG and IVIG in PIDD. **Results:** We enrolled 51 patients and the median ages were 10.3 and 17.5 years of IVIG and SCIG groups ($p<0.001$). The patients who received SCIG treatment were significantly older and the duration of treatment was longer than the IVIG group ($p=0.003$ and $p=0.004$,respectively). There was no significant difference in the frequency of hospitalization between the two groups (in IVIG and SCIG groups, 26.4% vs 5.8%,respectively) ($p=0.08$). The annual median number of infections in patients requiring outpatient treatment were 6.0 and 4.0 in the IVIG and SCIG groups ($p<0.001$). Although, the incidence of systemic side effects was statistically significantly higher in the IVIG group($p=0.002$), local side effects were significantly more frequent in the SCIG (35.9% vs. 5.9%,respectively)($p=0.012$). The total average costs incurred were statistically significantly higher in the group receiving IVIG in all three years compared to those receiving SCIG ($p<0.001$). **Conclusion:** SCIG treatment had more lower systemic adverse effects, cost, infection rates, antibiotic usage and duration of hospitalization than IVIG treatment in PIDD.

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Introduction

Primary immunodeficiency diseases (PIDD) are a group of rare and chronic conditions in which part of the body's immune system is missing or does not function correctly. PIDD results from genetic mutations affecting one or several components of the immune system, including cells and proteins. Children with PIDD commonly experience increased susceptibility to infections.[1] Over the half of patients (52%) of PIDDs are humoral immunodeficiencies. Immunoglobulin G (IgG) replacement therapy is the mainstay of treatment in many primary immunodeficiency diseases (PIDD) associated with humoral immune defects.[2]

IgG replacement therapy can be administered intravenously or subcutaneously. It has been shown that both administration methods effectively reduce the risk of acute and chronic infections.[3-5] Soon after administering the dose of IVIG, serum IgG concentration rises which is called serum peak IgG level. Until the next IVIG dose is administered, the serum concentration of IgG gradually decreases and then minimum serum concentration is obtained. The serum IgG trough level, defined as concentration preceding the next dose of immunoglobulin (Ig) infusion, has been regarded as an important guide to therapy. Serum IgG concentrations 600-700 mg/dl following IgG therapy have been recommended for adequate protection from serious infections in PIDDs.[2,3,5,6]

Higher concentrations of immunoglobulin formulations (>10%) have been developed over the past 25 years. Several clinical trials of subcutaneously administered infusions of immunoglobulin provided high serum trough levels of IgG and comparable protection from infection, while adverse events were reduced when compared to IVIG.[7,8] Studies have also demonstrated significant improvement in quality of life and treatment satisfaction as reported by PIDD patients due to the increased independence and scheduling flexibility associated with home-based, self-administered therapy. It is also reported that SCIG and IVIG treatments are similarly effective in preventing infections in PIDD patients.[4,9,10] This study was designed to evaluate the incidence of side effects, frequency of infections, duration of antibiotic usage, rate of infections requiring hospitalization and tolerability of subcutaneously administered SCIG and IVIG in children and adults with PIDD.

Material and Methods

Patient Selection

Patients in all age groups who were followed up between 01/01/2016 and 01/01/2019 dates with the diagnosis of PIDD and who received IVIG or SCIG treatment in the Tertiary Pediatric Immunology Unit were included in our study retrospectively.

The patients were contacted by phone and after information about the study was given to the parents, written/verbal consent was obtained from them who agreed to participate in the study.

Patients who could not be reached by phone and provided incomplete data were excluded from the study. Ethics committee approval was received by the Education and Research Hospital Local Clinical Research Ethics Committee (Date: 15/04/2019, Number: 2019-017).

Data Collection and Evaluation of Patients

Age, gender, age at diagnosis of PIDD, body weight, total duration of treatment, and diagnosis of the patients were recorded. The number of infections requiring hospitalization, length of stay in the intensive care unit and wards, the number of infections that can be treated on an outpatient basis, the duration of antibiotic usage, the side effects developed during their treatment, and the IgG intermediate values of the patients receiving IVIG and SCIG were analyzed. The costs of SCIG and IVIG treatments were compared by calculating the Ig preparations applied, the medical materials used, the nursing care costs (such as intravenous access, IV drug infusion) and hospitalization costs.

Since the body weights of the patients in the IVIG group and the SCIG group were different, the amounts of Ig preparations administered to the patients also showed differences. Therefore, in order to compare the two groups appropriately, while calculating the Ig preparation costs, the total cost of the preparations was calculated as the cost per kg by dividing the sum of the body weights.

Statistical Analysis

Data were analyzed using the program SPSS 25.0 (IBM, Armonk, NY: IBM Corp.). Mean ± standard deviation for parametric tests in presenting continuous variables; for non-parametric tests median and categorical variables were expressed as numbers and percentages. The conformity of the data to the normal distribution was examined with the Kolmogorov–Smirnov test. Chi-square analysis was used to analyze the differences between categorical variables. Mann Whitney U test used

for nonparametric variables. p<0.05 was considered statistically significant in all data analyses,

Results

Demographic and Clinical Characteristics

The median age of 51 patients included in the study was 12 years (min - max:1.5-29); 10.3 years of IVIG recipients and 17.5 years of SCIG group (p<0.001) (Table 1). The patients who received SCIG treatment were significantly older and the duration of treatment was longer than the IVIG group (p=0.003 and p=0.004, respectively) (Table 1). The majority of patients (66.6%) in both the IVIG and SCIG groups were receiving Ig therapy with the diagnosis of Common Variable Immunodeficiency (CVID) (Table 2). The frequency of Ig treatment and the dosage of Ig preparation in the IVIG and SCIG groups in the study are shown in Table 3.

Table 1. Demographic features of children and total treatment time.

	IVIG (n=34)	SCIG (n=17)
Gender *(F/M)*	19/15	7/10
Age (year) [median (*min-max*)]	*10.3 (*1.5 – 18.0*)	17.5 (*6.0 – 29.0*)
Diagnosis age (mo) [median (*min-max*)]	§53.0 (*3.0 – 144.0*)	120.0 (*14.0 – 180.0*)
Total treatment time (year) (mean ±SD)	5.10 ± 2.75	µ9.03 ± 5.73

F: Female, IVIG: Intravenous Immunglobuline, M: Male, max:Maximum, min:Minimum, mo:Month, SCIG: Subcutaneous Immunglobuline, SD:Standard deviation

*Patients were significantly older age in SCIG group (p<0.001).
§Diagnosis age were more higher in SCIG group than IVIG group (p=0.003).
µ Total treatment time was longer in SCIG group than IVIG group (p=0.004).

Table 2. Primary immundeficiencies of patients receiving IVIG and SCIG treatments.

Primary Immundeficiencies	IVIG [n *(%)*]	SCIG [n *(%)*]	Total [n *(%)*]
CVID	22 *(64.7)*	13 *(76.4)*	35 (68.6)
XLA	1 *(2.9)*	1 *(5.9)*	2 (3.9)
Ataxia-Telengiectasia	5 *(14.9)*	1 *(5.9)*	6 (11.8)
WAS	1 *(2.9)*	0	1 (1.9)
ALPS	2 *(5.9)*	1 *(5.9)*	3 (5.8)
CHS	1 *(2.9)*	0	1 (1.9)
IL-21 Receptor Deficiency	1 *(2.9)*	0	1 (1.9)
HyperIgM Syndrome	0	1 *(5.9)*	1 (1.9)
DOCK8 Lack	1 *(2.9)*	0	1 (1.9)

ALPS: Autoimmune Lymphoproliferative Syndrome, CHS: Chediak Higashi Syndrome, CVID: Common Variable Immunodeficiency, IVIG: intravenous immunglobuline, SCIG: subcutaneous immunglobuline, XLA: X-linked agammaglobulinemia, WAS: Wiskott-Aldrich Syndrome

Table 3. Evaluation of Infusions in terms of Number and Dose According to Immunoglobulin Administration Method

	IVIG (n=34)	SCIG (n=17)
Infusion Frequency, n (%)		
7th day	0	12 *(70.6)*
15th day	0	5 *(29.4)*
21th day	3 *(8.8)*	0
28th day	31 *(91.2)*	0
Ig dosage (g/kg) (mean ±SD)	0.48±0.18	0.39±0.13*
Infusions per patient /year [median (*min-max*)]	12.0 *(12.0-17.0)*	48.0 *(24.0-48.0)*

IVIG: intravenous immunglobuline,
SCIG: subcutaneous immunglobuline
*There was no statistically significant difference between SCIG and IVIG groups (p=0.128).

Efficacy of the Treatment

At the beginning of Ig treatment, serum IgG median values in IVIG and SCIG groups were 666 mg/dl (min - max: 500 mg/dl and 1100 mg/dl) and 640 mg/dl (min-max: 544 mg/dl and 1600 mg/dl), respectively (p>0.05). In addition, serum IgG median values of IVIG group at 6 and 12 months after treatment were 875.5 mg/dl and 888 mg/dl. Serum IgG median values of SCIG group at 6 and 12 months after treatment were 900 mg/dl and 902 mg/dl, respectively (p=0.690 and p=0.490, respectively)(Table 4). It was found that 19.6% (n=10) of the patients had an infection requiring hospitalization. There was no significant difference in the frequency of hospitalization between the two groups (in IVIG and SCIG groups, 26.4% vs 5.8%, respectively) (p=0.08). Median hospitalization times were 7 days (min-max: 5-10) in the

Table 4. Serum IgG levels according to ımmunoglobulin administration method.

Serum IgG Level (mg/dL)	IVIG	SCIG
Basal [median (*min-max*)]	666 *(500-1100)*	640 *(544-1600)**
6th month [median (*min-max*)]	875.5 *(796-1664)*	900 *(788-1400)*&
12th month [median (*min-max*)]	888 *(520-1340)*	902 *(666-1020)*µ

There was no statistically significant difference between SCIG and IVIG groups
(*p=0.413) (&p=0.490)(µ p=0.490)
Mann-Whitney U Test

IVIG group, whereas only one patient in the SCIG group required 5-day hospitalization. In addition, none of the patients in the SCIG group required hospitalization in the intensive care unit while only one patient in the IVIG group needed intensive care due to severe pneumonia. The annual median number of infections in patients requiring outpatient treatment was 6 (min-max:3-12) in the IVIG group and 4 (min-max:1-7) in the SCIG group (p<0.001). The types of infections in both groups are shown in table 2. In our study, the incidence of pneumonia in the IVIG group was statistically significantly higher than the SCIG group (58.8% vs 23.5%, respectively) (p=0.037). The most common infections were determined as upper respiratory tract infections, lower respiratory tract infections and other types of infections (such as AGE, AOM, UTI). In addition, the duration of antibiotic usage of the patients was found to be 49 days per year (min- max: 20- 120) in the IVIG group; It was 20 days in the SCIG group (min - max:2 - 40) (p<0.001).

Adverse Reactions

Systemic or local side effects were observed with a frequency of 67.6% (n=23) in the IVIG group and 35.3% (n=6) in the SCIG group (p=0.058). The incidence of systemic side effects was statistically significantly higher in the IVIG group (p=0.002)(Table 5). On the other hand, local side effects were significantly more frequent in the SCIG group (35.9% vs. 5.9%, respectively) (p=0.012) (table 5). Aseptic meningitis and convulsions, which are rare side effects of Ig therapy, developed in two patients who received IVIG therapy.

Table 5. Cost of immunoglobulin administration by years (in USD)

	IVIG (mean ±SD)	SCIG (mean ±SD)
1th year		
Ig preparation cost	682.81 ± 75.5	563.64 ± 62.3
Hospitalization cost	24.02 ± 1.73	-
Nurse care service	71.55 ± 5.16	5.44±0.41
Infusion Set/ Butterfly Set	21.72 ± 1.56	27.22± 1.56
Total cost	800.11 ± 78.33	596.31 ± 64.25
2th year		
Ig preparation cost	682.81 ±75.5	563.64 ± 62.3
Hospitalization cost	24.02 ± 1.73	-
Nurse care service	71.55 ± 5.16	-
Infusion Set/ Butterfly Set	21.15 ±3.72	27.22± 1.56
Total cost	799.54 ±77.95	590.86 ± 63.87
3th year		
Ig preparation cost	682.81 ± 75.5	563.64± 62.3
Hospitalization cost	24.02 ± 1.73	-
Nurse care service	71.55 ± 5.16	-
Infusion Set/ Butterfly Set	21.15 ± 3.72	27.22± 1.56
Total cost	799.54 ± 77.95	590.86 ± 63.87

IVIG: intravenous immunglobuline,
SCIG: subcutaneous immunglobuline

Cost Evaluation

The total costs of the patients are shown in Table 6. The total average costs incurred were statistically significantly higher in the group receiving IVIG in all three years compared to those receiving SCIG (p<0.001)

Discussion

The data from files of 34 patients receiving IVIG therapy and 17 patients receiving SCIG therapy, in the age range from infancy to adulthood with PIDD diagnosis, were evaluated retrospectively in our study. Our aim was to evaluate our patients who received IVIG and SCIG treatment in terms of side effects, infection frequencies, cost effectiveness, and compare them with the literature. In order to prevent infections in PIDD patients, it is recommended to keep the mean serum IgG value at the level of 700-800 mg/dl.11 It has been supported by various studies that SCIG treatment is as effective as IVIG in preventing the development of infections and keeping the serum IgG level at the desired level in patients with PIDDs.[12,13] In previous studies, it was recommended to keep the minimum threshold value of serum IgG at 500 mg/dl in order to prevent infections in PIDD patients.[14-17] In recent clinical studies, it is recommended to target the serum IgG level at higher levels such as >800 mg/dl,[18] and to keep it in the range of 650-1000 mg/dl in the latest guidelines.[19] In our study, when IVIG and SCIG groups were compared, no significant difference was found between the median serum IgG intermediate values measured at the beginning of Ig therapy and at the 6th and 12th months after treatment. Our study's results were similar to the literature. In a retrospective study by Kobayashi et al., the annual febrile infection rate per capita was 0.20 and the hospitalization rate was 0.83 in pediatric patients diagnosed with PIDD (n=38). The most common infections were upper respiratory tract infections, while other frequent infections were stated as lower respiratory tract infections, gastrointestinal tract infections and otitis in Kobayashi's study.[21] In the retrospective study of Ochs et al., 49 patients from all age groups diagnosed with PIDDs were included and the annual infection rate was 4.43/patient. The most frequently reported infections were sinusitis, upper respiratory tract infections, bronchitis, rhinitis and conjunctivitis. Four of the patients had an infection requiring hospitalization and had a total of 12-day service admissions per year.[22] In this study, the median number of infections in patients receiving outpatient treatment was 6 per year in patients receiving IVIG; it was 4 per

year in the SCIG group. In our study, the most common infections were determined as upper respiratory tract infections, lower respiratory tract infections and other types of infections (such as AGE, AOM, UTI), respectively, similar to the literature. In our study, it was determined that 10 of 51 patients had an infection requiring hospitalization. Of these, 9 were in the IVIG group, while 1 was a patient receiving SCIG.

In various studies comparing SCIG and IVIG, it has been shown that less systemic side effects are seen receiving the SCIG treatment. Eltan et al.'s 20 pediatric patients with PID who were receiving IVIG were switched to SCIG treatment and compared in terms of side effects. It was stated that none of the patients receiving IVIG and SCIG developed serious systemic side effects. Local side effects were not observed during IVIG treatment, and systemic side effects did not develop in patients who switched to SCIG treatment. Local side effects (most commonly pain, redness, swelling at the injection site) were observed in 95% of the patients. It has been reported that there is a significant decrease in the development of systemic side effects when switching from IVIG to SCIG.[23] In the study of Gür-Çetinkaya et al., 9 patients with PIDDs in the pediatric age group were evaluated. After switching to SCIG treatment, local side effects developed in all patients and the most common local side effects were swelling, redness and pain at the injection site. It was stated that no systemic or serious side effects developed.[24]

In our study, it was observed that systemic or local side effect developed in 23 of the patients who received IVIG treatment and 6 of the patients in the SCIG group. The risk of developing systemic side effects was found to be significantly higher in patients who received IVIG treatment compared to the SCIG group. Convulsion, which is one of the rare systemic side effects of Ig therapy, was detected in one patient in the IVIG group. Aseptic meningitis, which is also a rare side effect, developed in one of the patients who received IVIG treatment. Based on the data obtained from our study, it can be said that systemic side effects can be reduced with SCIG treatment. Although no systemic or serious side effects develop with SCIG, it has been determined that more local side effects can be seen. These results are in line with similar studies and show that SCIG treatment may be more reliable than IVIG in terms of side effects.

Since SCIG is a form of treatment that the patient can apply on her own after training, it reduces the cost by reducing hospital admissions. In the study of Martin et al., 3-year costs per patient of IVIG and SCIG treatments were calculated. While the total cost per patient in the first 3 years of IVIG treatment was $7714, it was calculated as $1978 in SCIG treatment. Therefore, it was stated that by switching to SCIG treatment, a gain of $5736 per patient could be achieved in 3 years.[25] In this study, similar to the literature, the mean cost in the group receiving SCIG was significantly lower at all three years than the group receiving IVIG. In the 2nd and 3rd years of the treatments, there were no nursing care costs in the patients who received SCIG treatment, since the patients could apply the treatment themselves with the training given in the first year. However, in the IVIG group, it was thought that the cost increased significantly due to extra expenses such as hospitalization and nurse care costs.

Conclusion

SCIG is as effective and safe as IVIG in the treatment of patients with PIDDs. Although local side effects can be seen with SCIG treatment, the risk of developing systemic side effects can be reduced. In addition, SCIG is a treatment option that increases the quality of life because it can be taken at home by the patient alone and decreases hospital costs by reducing hospital admissions.

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RESEARCH ARTICLE

Classification Of Post COVID-19 Pulmonary Findings Evaluated By Computed Tomography

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Abstract

Introduction: The COVID-19 pandemic has affected millions of people worldwide. Some patients with COVID-19 pneumonia have residual Computed Tomography (CT) findings in the lungs due to lingering symptoms for weeks after infection. Given the widespread impact of the COVID-19 pandemic, it is crucial to recognize and classify these findings. The aims of study is to identify and classify patients post COVID-19 chest CT findings according to a pattern.
Methods: : We examined 74 patients over the age of 18 who tested positive for COVID-19 using Polymerase Chain Reaction (PCR) and underwent multiple chest CT scans at intervals after their first diagnosis. Patients were classified as having non-specific interstitial pneumonia (NSIP), possible usual interstitial pneumonia (UIP), organizing pneumonia (OP), or no distinctive pattern. We also evaluated demographic data of the patients.
Results: A total of 74 patients were included in the study, with 57 (77%) males and 17 (23%) females. The median age of the participants was 64 years. Of these, 47 (63.5%) had NSIP, 6 (8.1%) had possible UIP, 3 (4.1%) had OP pattern, and 18 (24.3%) patients had no distinctive pattern.
Conclusion: Studies using control chest CT examinations 3-12 months after COVID-19 infection have shown residual lung findings at varying rates. In our study, most patients exhibited NSIP pattern, with fewer OP and possible UIP pattern findings. One fourth of the patients had no distinctive pattern.

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Introduction

The COVID-19 (Coronavirus Disease 2019) pandemic began in China in 2019 and swiftly became a part of our lives in 2020, infecting millions of people and resulting in numerous deaths.[1] Although the infection rate has significantly decreased in recent times due to vaccinations and natural immunity, the disease has not been entirely eradicated. Furthermore, there is a possibility of a resurgence with new variants. Recent studies indicate that approximately 20% of cases have a severe profile requiring hospitalization, with acute viral pneumonia and associated acute respiratory distress syndrome (ARDS) being the most common causes of morbidity and mortality.[2] Some patients with COVID-19 pneumonia experience weakness, fatigue, shortness of breath, exertional dyspnea, and a persistent cough that lasts for weeks, prompting them to seek care at COVID follow-up outpatient clinics.[3] The estimated rate of these complaints during a one-year follow-up is approximately 40%.[4] According to some studies, post-infectious complications are observed in about 70% of cases, especially following severe COVID-19 infection, with pulmonary fibrosis being one of the most significant complications.[5] The British Medical Journal guideline defines prolonged COVID if an infection lasts longer than 4 weeks and post-COVID syndrome if it lasts longer than 12 weeks.[6-7]

It is known that SARS-CoV-2 causes pulmonary damage through multiple mechanisms, and lung CT findings during the acute phase of the disease have been clearly defined.[8] The pulmonary pathology in the acute phase of the disease is diffuse alveolar damage, which is considered to be a factor in the development of post-COVID-19 fibrosis, as the final stage of diffuse alveolar damage leads to fibrosis.[9-10] Organized pneumonia may emerge as a long-term sequelae of acute COVID-19 infection.[11] In some severe cases, histopathologic alterations associated with fibrosis have been reported,[12] and other studies have shown the occurrence of usual interstitial pneumonia, desquamative interstitial pneumonia, and acute organized pneumonia patterns in the patient group with residual findings after COVID-19 pneumonia.[13-14] According to another study, there is a stronger association between Post-COVID-19 pulmonary fibrosis and the progression of the disease, particularly involving factors like the presence of pneumonia and the persistence of positive PCR tests for more than four weeks.[15]

The issue to be addressed pertains to the timing and extent of regression in pulmonary findings, if any, within the context of post-COVID-19 recovery. Questions arise regarding the persistence of residual lung alterations upon completion of the recovery process. Should such alterations endure, what specific manifestations can we anticipate? Furthermore, we must investigate the clinical relevance of these pulmonary changes as opposed to their status as purely radiological observations. Additionally, when conducting long-term follow-up chest CT examinations in these patients, there is a legitimate concern that these residual findings may introduce diagnostic challenges, particularly in cases where comprehensive patient medical histories are unavailable. Despite the existence of numerous publications on this subject, a definitive consensus remains elusive.

Previous experiences with the SARS-CoV-1 and MERS outbreaks indicated that very few patients with these diseases developed chronic pulmonary alterations. However, it's crucial to note that the scale of patients affected during those outbreaks was considerably smaller when compared to the SARS-CoV-2 pandemic. While the 3% rate of chronic pulmonary alterations for SARS-CoV-1 may appear low, it becomes a matter of significance when considering the enormous number of individuals infected by SARS-CoV-2. Furthermore, there is currently no universally accepted consensus regarding the rate of such alterations for SARS-CoV-2.[16-17]

Our purpose in this study is to identify the pulmonary parenchymal alterations that may develop after COVID-19 pneumonia, identify fibrosis symptoms that may have clinical significance for the patient, and reveal a possible post-COVID lung disease pattern by comparing it with the findings in previously recognized interstitial pneumonia with fibrosis. This will enable us to establish a classification and make it easier to recognize thorax CT examinations of these patients in the following years.

Material and Methods

Study Approval and Participants

This study obtained approval from the ethics committee, and the institutional review board waived the requirement for written informed consent, thereby confirming the retrospective nature of the research. The study comprised individuals aged 18 and above who had positive COVID-19 PCR test and sub-

sequently received follow-up care at COVID outpatient clinics during the period spanning July 2020 to May 2021. Eligible participants were those presenting ongoing complaints of chest pain, shortness of breath, fatigue, and persistent cough. A substantial portion of these individuals had undergone multiple chest CT examinations subsequent to receiving a positive PCR test result for COVID-19. A total of 200 patients were enrolled in the study. These participants were classified into two groups based on their chest CT findings: those with normal findings and those with abnormal findings. Among the initial 200 patients, 122 individuals displaying normal chest CT findings were excluded from the study. Consequently, the primary focus of the analysis was directed toward the remaining 78 patients who exhibited abnormal chest CT findings, with the objective of discerning patterns indicative of fibrosis or possible fibrosis. An additional four patients were subsequently excluded from the study due to findings that appeared to be associated with non-COVID-related factors, such as lung masses, suspected metastases, or potential asbestos exposure.

CT Indication

In the post-COVID-19 era, the indications for chest CT scans exhibit variability, albeit with a predominant focus on the presence of persistent or newly emergent respiratory symptoms. These symptoms encompass phenomena such as dyspnea, chest pain, or recurrent infections. Furthermore, the decision to undertake a chest CT scan was subject to influence from preliminary assessments conducted in primary care or emergency care settings. In these contexts, suspicions regarding potential abnormalities were grounded in initial clinical evaluations and radiological appraisals. Several follow-up CT studies were conducted as an integral component of the patients' routine clinical surveillance, notably following the initial CT scan that had delineated the presence of sequela lesions. These ensuing studies were subsequently incorporated into our data compilation efforts. It is crucial to underscore that the determination of these indications was guided by the prevailing standard clinical guidelines and protocols in force during the patients' assessments.

CT Imaging Procedure

A standardized non-contrast chest CT scan was conducted using equipment from GE Healthcare in Chicago, Illinois, USA. The scans were performed with patients in the supine position during the inspiratory phase. The scan parameters included a tube voltage of 100kV, a range of 50-399 milliampere-seconds (mAs), and a section thickness of 1.3 millimeters.

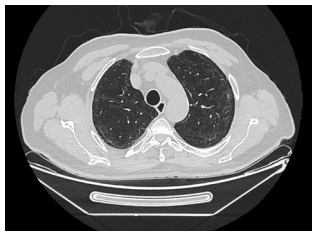
CT Examination and Analysis

The CT scans were carefully examined, encompassing a wide range of features such as ground-glass opacity (GGO), consolidation, irregular subpleural patterns, traction bronchiectasis, the presence of a honeycombing sign, volume loss, involvement of perilobular regions, nodules, parenchymal bands, subpleural striations, subpleural preservation, and subsegmental atelectasis. We also conducted a comprehensive analysis of the distribution patterns of these findings. The selection of these specific features for analysis during chest CT examinations was based on our extensive experience with interstitial lung diseases and the standardized terminology provided by the Fleischner Society for chest scanning.

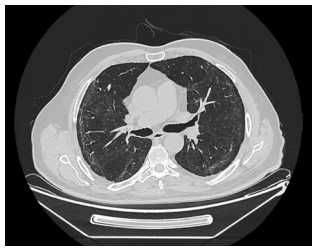
Classification of Patients

Patients underwent classification into distinct categories, which encompassed non-specific interstitial pneumonia (NSIP), possible usual interstitial pneumonia (UIP), organized pneumonia (OP), or the absence of a distinctive pattern. The criteria employed for classification included the presence of lower lobe and peripheral/peribronchovascular predominant ground glass opacities, irregular reticulations, subpleural preservation, and bronchiectasis/bronchioloectasis for NSIP (figures 1a,1b and 1c).

1a



1b



1c

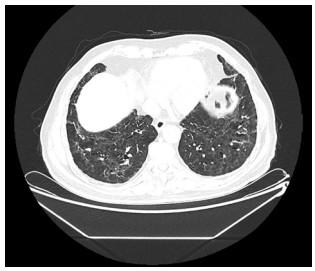
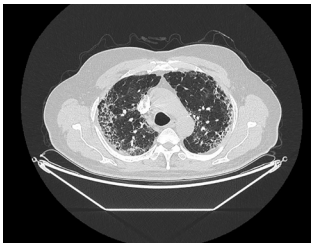


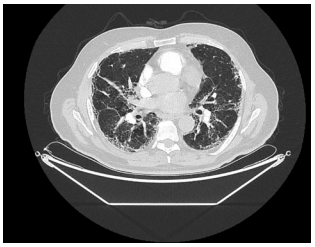
Figure 1: Images of a post-COVID-19 patient's upper zone (a), middle zone (b), and lower zone (c) at 5 months, showing subpleural sparing, subpleural reticular opacities, and peripheral GGO in the upper lobes, as well as GGO, subpleural reticular opacities, and parenchymal bands in the lower lobes. The patient was evaluated as having a non-specific interstitial pneumonia (NSIP) pattern.

UIP was identified by the predominance of irregular reticulations, honeycombing cysts, and volume loss, primarily in the lower lobes and peripheral regions (figures 2a,2b and 2c).

2a



2b



2c

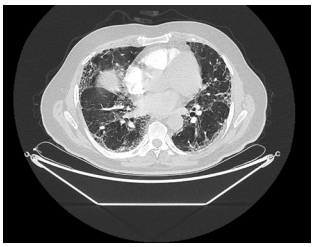
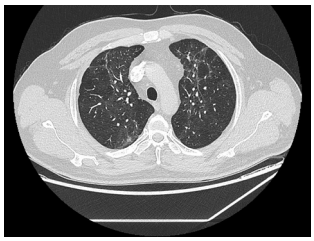


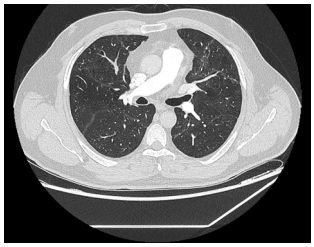
Figure 2: Images of a post-COVID-19 patient's upper zone (a), middle zone (b), and lower zone (c) at 5 months, showing peripheral reticular opacities and honeycombing in all lobes, as well as architectural distortion in the lower lobes. The patient was evaluated as having a usual interstitial pneumonia (UIP) pattern.

OP was characterized by lower lobe predominant consolidation/ground glass opacities and perilobular opacities displaying peripheral and peribronchovascular distribution. Findings that defied classification within these established categories were designated as "no distinctive pattern" (figures 3a,3b and 3c).

3a



3b



3c

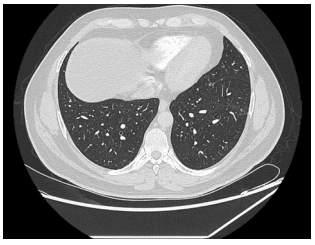


Figure 3: Images of a post-COVID-19 patient's upper zone (a), middle zone (b), and lower zone (c) at 7 months, showing bilateral upper lobe parenchymal bands, traction bronchiectasis, and peripheral ground-glass opacities (GGO). Note that the lower lobes appear normal. The patient was evaluated as having no distinctive pattern.

Demographic and Clinical Data

Demographic data, including smoking history, comorbid conditions, hospitalization, intensive care unit admissions, mechanical ventilation, steroid usage, and antiviral treatments, underwent meticulous analysis.

Radiological Assessment

Chest CT examinations were performed by two radiologists, each possessing over a decade of experience in chest CT imaging. In instances where conflicting findings emerged, a third radiologist, specialized in chest radiology, was consulted to facilitate consensus.

Statistical Analysis

Data were subjected to statistical analysis utilizing the IBM SPSS Statistics Standard Concurrent User V26 software package, developed by IBM Corporation in Armonk, New York, USA. Descriptive statistics were presented in terms of both the numerical count (n) and percentage (%) values. Relationships between categorical variables were assessed employing the Fisher's Exact Test and Chi-Square test, with statistical significance being determined by a p-value of less than 0.05.

Results

Study Population and Demographics

The study enrolled a total of 74 patients, comprising 57 (77%) males and 17 (23%) females. The median age of the patient cohort was 64 years, with a mean age of 64.15 ± 9.22 years. The median interval between the patients' initial COVID-19 infection and their subsequent CT examinations was determined to be 7 months (Table 1).

Table 1. Descriptive Statistics on Patient Information

	Mean ± SD	*Median (Min-Max)*
Age (year)	64,15±9,22	64 (47-83)
Evaluated CT Time (month)	7,64±2,84	7 (4-12)

SD: Standard Deviation, CT: Computed Tomography

Prevalence of Comorbidities and Medical Interventions

A noteworthy proportion of patients reported comorbidities, including hypertension (48.6%), diabetes mellitus (17.6%), and heart disease (23.0%).

Additionally, the majority of patients had no history of smoking (54.1%), chronic kidney disease (94.6%), cancer (98.6%), or Chronic Obstructive Pulmonary Disease (COPD) (90.5%).

Concerning medical interventions, a substantial number of patients underwent hospitalization (94.6%) during the course of their illness, and a smaller percentage necessitated mechanical ventilation (6.8%). Corticosteroid treatment was administered to the majority of patients (87.8%), while antiviral treatment was almost universally employed (98.6%) among the study cohort (Table 2).

Table 2. Descriptive Statistics on Patient Characteristics

		N	*%*
Smoking	No	40	54,1
	Yes	34	45,9
Hypertension	No	38	51,4
	Yes	36	48,6
Diabetes Mellitus	No	61	82,4
	Yes	13	17,6
Chronic Kidney Disease	No	70	94,6
	Yes	4	5,4
Cancer	No	73	98,6
	Yes	1	1,4
COPD	No	67	90,5
	Yes	7	9,5
Heart Disease	No	57	77,0
	Yes	17	23,0
Hospitalization	No	4	5,4
	Yes	70	94,6
Intensive Care Unit Stay	No	40	54,1
	Yes	34	45,9

N: Number, COPD: Chronic Obstructive Pulmonary Disease

Distribution of CT Findings

As all of our patients were drawn from a population exhibiting pathological alterations in lung parenchyma, the majority presented with multiple CT findings, including ground-glass opacities, subpleural reticulation, traction bronchiectasis, and perilobular involvement. Ground-glass opacities (GGO) were the most prevalent CT finding (89%), followed by subpleural reticulation (64%), traction bronchiectasis (44%), perilobular involvement (31%), and subpleural sparing (18%). Nodules (2%), consolidation (4%), and honeycombing (7%) were the least frequently encountered findings.

Moreover, we scrutinized the distribution of these findings within the lung to establish a discernible pattern. GGO was predominantly located peripherally (55%), followed by an axial plane distribution (31%), and central localization (2.7%). In terms of craniocaudal distribution, GGO within the lung zones exhibited the following patterns: 55% distributed throughout all lung zones, 24% displayed predominant involvement in the middle and lower zones, and 9.5% exhibited predominant involvement in the upper zones. Subpleural reticulations were most commonly observed in the middle-lower zone (41%), while traction bronchiectasis predominated in the middle-lower zone (32%) (Table 3).

Predominant CT Findings

The most frequently observed pattern among our patients entailed irregular reticulation, perilobular opacities, and ground-glass opacities, primarily situated subpleurally. However, in some instances, these findings exhibited peribronchovascular distribution in the lower lobe levels and occasionally extended to involve the upper lobes, albeit with a slightly greater predilection for the lower lobes. These features were sometimes accompanied by predominant traction bronchiectasis in the peripheral and lower lobe regions. Honeycombing, consolidation, volume loss, and parenchymal bands were infrequently identified. The CT characteristics of the disease predominantly suggested a non-specific interstitial pneumonia (NSIP) pattern. Additionally, perilobular involvement and isolated areas of consolidation contributed to the organized pneumonia component. The usual interstitial pneumonia (UIP) or UIP-like pattern was exceedingly rare. In this study, we categorized 63.5% of the patients under the classification of fibrotic NSIP (Table 3).

Table 3. Descriptive Statistics on Clinical Findings

		N	*%*
Ground-Glass Opacity (GGO)	No	8	10,8
	Yes	66	89,2
Ground-Glass Opacity (GGO) Distribution	None	8	10,8
	Peripheral	41	55,4
	Central	2	2,7
	Random	23	31,1
Ground-Glass Opacity (GGO) Zone	None	8	10,8
	Upper Zone	7	9,5
	Middle-Lower Zone	18	24,3
	All Zone	41	55,4
Consolidation	No	70	94,6
	Yes	4	5,4
Subpleural Irregular Reticulation	No	10	13,5
	Yes	64	86,5
Subpleural Irregular Reticulation Distribution	None	10	13,5
	Upper Zone	10	13,5
	Middle-Lower Zone	31	41,9
	All Zone	23	31,1
Traction Bronchiectasis	No	30	40,5
	Yes	44	59,5
Traction Bronchiectasis Distribution	None	30	40,5
	Upper Zone	8	10,8
	Middle-Lower Zone	24	32,4
	All Zone	12	16,2
Honeycomb	No	67	90,5
	Yes	7	9,5
Volume Loss	No	72	97,3
	Yes	2	2,7
Perilobular Opacity	No	43	58,1
	Yes	31	41,9
Nodule	No	72	97,3
	Yes	2	2,7
Parenchymal Bands	No	60	81,1
	Yes	14	18,9
Subpleural Lines	No	46	62,2
	Yes	28	37,8
Subpleural Sparing	No	56	75,7
	Yes	18	24,3
Subsegmental Atelectasis	No	59	79,7
	Yes	15	20,3
Pattern	No Distinctive Pattern	18	24,3
	Fibrotic Nonspecific Interstitial Pneumonia (NSIP)	47	63,5
	Possible Usual Interstitial Pneumonia (UIP)	6	8,1
	Organising Pneumonia (OP)	3	4,1

N: Number, GGO: Ground Glass Opacities, NSIP: Nonspecific Interstitial Pneumonia, UIP: Usual Interstitial Pneumonia, OP: Organising Pneumonia

Patients exhibiting a "no distinctive pattern" displayed irregular reticulation and ground-glass opacities, with a more pronounced presence in the upper lobes and peripheral zones.

Discussion

Thorax CT findings related to COVID-19 infection have now been described in detail, and current research is focused on post-COVID pulmonary alterations. Studies on this subject are being conducted with CT findings and pulmonary function tests obtained at various times after COVID-19 infection, and our knowledge is growing. The most critical question in this regard is when and how much the findings will improve after COVID-19 infection. Studies have shown that most of these findings regress or even completely resolve, especially on follow-up CT examinations after one year. However, residual abnormalities persist in some patient groups. Considering the millions of people infected with COVID-19, this group of patients is not a minority. Therefore, the following questions arise: are these residual abnormalities true fibrotic alterations affecting pulmonary function, or are they insignificant sequelae? Another important question is, just like tuberculosis infection, which was once widely distributed and whose sequelae are now seen on thorax CT examinations, will these alterations be observed on thorax CT examinations for years to come, and will they cause confusion from time to time? Certainly, such questions will be answered in time and through detailed studies. It is the latter question that we try to answer and outline in the present study. It is an effort to look for a possible pattern for pulmonary alterations after COVID-19 infection.

Consistent with previous studies, most of the patients in the study were elderly (mean age 65), and the majority of them were male (77%). The patients were analyzed with CT examinations taken an average of 7 months after they had COVID-19 infection.[18-19]

In various studies, residual lung anomalies after COVID-19 infection have been reported, ranging from a minimum of 9-23% to a maximum of 72-84% .[19-20]

In a study by Bocchinio et al., the CT findings of 84 patients at 3, 6, and 12 months after COVID-19 infection were compared. The study recorded monthly alterations in imaging features such as ground-glass opacity (GGO), consolidation, pleural-parenchymal bands, linear atelectasis, bronchiectasis/bronchiole-

ctasis, reticulation, and honeycombing. While 100% of patients had GGO at baseline, the rate decreased over the months, reaching 20% at month 6. In the 12th month, it decreased to 2%. Consolidation was not observed in any patient after 6 months. GGO and consolidation were mostly diffuse, whereas, in those with focal distribution, the findings were predominant in the lower lobe. In the same study, fibrosis/fibrosis-like findings were found in 50% of the patients in the first 3 months and 42% in the 6th month. The findings were predominant in the lower lobe and periphery. Residual fibrotic alterations were detected in 5% of patients at the end of the 12th month (19). As in our study, the predominant finding in the aforementioned study was GGO with lower lobe peripheral predominance. In our study, we found 89% GGO, 5% consolidation, 86% reticulation, 59% traction bronchiectasis, and 18% parenchymal bands. The reason for such high values is that our patient group was selected from those with pathologic chest CT findings. However, in this study, we aimed to emphasize the possibility of residual thorax CT findings following COVID-19 and to fit them into a pattern.

In a meta-analysis of 15 studies and 3134 cases including thorax CT findings observed approximately 12 months after COVID-19 pneumonia by Watanabe et al., residual lung abnormalities were found in approximately 33% of patients. The most common finding was GGO and fibrosis-like alteration (21%). The other findings were bronchiectasis (10%), interlobular septal thickening (8%), reticulation (6%), and consolidation (3%). The residual findings were similar to our study, but no clear pattern was reported in these studies.[21]

In a study by Besutti G. et al., 6-7 months follow-up thorax CT examinations of 405 patients were analyzed. They classified CT findings as resorbed anomalies, residual non-fibrotic anomalies, and residual fibrotic anomalies. Complete or near complete resolution of lung anomalies was present in 55.6% of patients. Residual non-fibrotic anomalies were 37.5%. The most common finding was GGO with 35.1%, followed by bronchiectasis with a periferal predominant distribution in 12.8% of patients, perilobular opacities in 7.9%, and other anomalies (such as parenchymal band, consolidation) in less than 3%. Researchers classified 67.7% of patients as non-fibrotic NSIP and 32.3% as mixed NSIP-OP patterns in the no-fibrotic group.[18] Residual fibrotic anomalies were found in 6.9% and most of them were classified as fibrotic NSIP as a pattern and very few of them were identified as possible UIP and UIP patterns.[18] In our study, similar findings to the above study were observed and we conclude that the most common pattern is the NSIP-like pattern. Additionally, there was an unclassifiable group that did not resemble the patterns we know in our study, and upper lobe predominance or diffuse lung involvement was mainly observed.

The limitations of our study are that it is a single-center, retrospective study and has a relatively small number of patients. Moreover, the examination of residual anomalies and possible fibrosis in the lung following COVID-19 infection was conducted only with CT, and we did not have data on pulmonary function tests and the 6-minute walk test. Another challenge is the definition of pulmonary fibrosis. The issue may include some individual differences. Although various studies have emphasized similar features with slight differences, there is no common consensus yet. Another challenge is whether these findings will be permanent or not. At later stages, the findings may regress, remain stable or progress to progressive fibrosis. In this case, we may need a new nomenclature and classification, time will tell.

Conclusion

In conclusion, In studies conducted with control thorax CT examinations between 3-12 months following COVID-19 infection, it was detected that there were residual findings in the lung at various rates. Naturally, not all of these can be classified as fibrosis. However, there are certainly some long-term or permanent alterations in the lung, especially after severe COVID-19 infection, and this is manifested in the patient's clinic. Considering that millions of people worldwide are affected by this infection, it is likely that post-COVID lung findings will be common in the years to come. Our purpose when we started this study was to see if there was a method to identify these patients in a pattern similar to tuberculosis infection. In our study, we found that most of the patients had NSIP-like findings in the first year, while OP and UIP pattern findings were less common. A quarter of the patients had findings that did not match.

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RESEARCH ARTICLE

Early Period Results for Endovascular Stent Grafting in Abdominal Aortic Aneurysms: A Single-Center Experience

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Abstract

Introduction: In the management of abdominal aortic aneurysm (AAA), endovascular aneurysm repair (EVAR) presents as a superior alternative to conventional surgery, especially for elderly patients with elevated surgical risks and accompanying comorbidities. This study aimed to examine the early outcomes of AAA patients who underwent EVAR. **Methods:** A total of 33 patients diagnosed with AAA who underwent EVAR were evaluated retrospectively. In every patient, the indication for the EVAR procedure was an abdominal aorta diameter exceeding 5.5 cm or over 5 cm when accompanied by additional comorbid factors. During the 1-year follow-up period for the patients, data on early-phase outcomes, lengths of stays in ICU and the hospital, and post-procedure complications were collected. **Results:** In 5 of the patients who underwent EVAR, both iliac artery aneurysm and AAA were present, while in 28, only AAA existed. The median length of ICU stay was 13 hr, and the median length of hospital stay was 3 days. In 12% of the patients, Type I-III endoleak was detected. In the follow-ups examinations, two patients without detected endoleaks manifested lower extremity ischemia or rupture. The total complication rate was 21.2%. There were no mortality cases during the early follow-up period. **Conclusion:** EVAR, in older patients with coexisting comorbidities, offers advantages in diminishing durations in intensive care and hospital stays, potentially boosting early survival outcomes. However, the results from our single-center study indicated that a substantial fraction of patients are susceptible to complications during the early postoperative period.

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Introduction

Abdominal aortic aneurysm (AAA) is a pathologic condition characterized by an enlargement of the abdominal aorta measuring 3.0 cm or greater, which can lead to the aorta's potential rupture.[1] The majority of AAAs are asymptomatic, frequently detected incidentally during imaging procedures for other indications, and pose a significant risk of mortality.[2] The etiology of AAA is multifactorial, with male gender, tobacco usage, age exceeding 65, and coexisting conditions such as hypertension, coronary artery disease, and peripheral vascular diseases being significant contributors.[3]

In young patients with a life expectancy exceeding 15 years, devoid of additional risk factors, without anatomical constraints like horseshoe kidney or abdominal stoma, and without any comorbidities, open surgery is advised for aneurysm repair.[4] In the early 1990s, endovascular aneurysm repair (EVAR) emerged as a fusion of vascular surgery and interventional radiology, serving as a complement to open surgery. Its aim was to address a higher-risk patient group. Due to its minimally invasive nature and success in the early period, it has become a strong alternative to open surgery.[5]

EVAR is associated with situations such as the risk of permanent rupture, the risk of re-intervention, and the need for continuous surveillance.[6,7] In addition to these, the data on early, mid-term, and long-term outcomes of EVAR are still not comprehensive enough. This study aimed to examine the early outcomes of AAA patients who underwent EVAR.

Material and Methods

This retrospective study included patients diagnosed with AAA who underwent EVAR in Izzet Baysal Training and Research Hospital Cardiovascular Surgery Clinic between January 2016 and July 2019. The study initiated with the approval of the Bolu Abant Izzet Baysal University Clinical Resarches Ethics Committee (Date: 18.09.2023, Decision No: EA-1568) and was carried out in accordance with relevant ethical guidelines and the Declaration of Helsinki (revised in 2013, Brazil). The need for informed consent was waived by the local ethics committee due to the retrospective design.

A total of 33 patients diagnosed with AAA who underwent EVAR were evaluated retrospectively. The diagnoses of the patients and the graft sizes were determined based on the results of the 64-slice computed tomography angiography. In every patient, the indication for the EVAR procedure was an abdominal aorta diameter exceeding 5.5 cm or over 5 cm when accompanied by additional comorbid factors. All procedures were performed in the interventional angiography laboratory (GE Innova 2100). An operating room had been kept available during each procedure to address any unforeseen need for emergency surgical intervention. After anesthesia was administered, a bilateral femoral artery dissection had been conducted, preparing both main femoral arteries. After administering anesthesia, a bilateral femoral artery dissection was performed, preparing both main femoral arteries. An arteriotomy was then performed, and through the transfemoral approach, a suitable endovascular graft was inserted. Every patient was treated using the Endurant (Medtronic, Minneapolis, MN, USA) EVAR graft. After the procedure, a control angiography was performed to confirm the graft was open and the aneurysm was fully sealed (Figure 1). The arteriotomy in the femoral artery was closed, and patients were monitored in intensive care unit (ICU) for one day following the procedure.

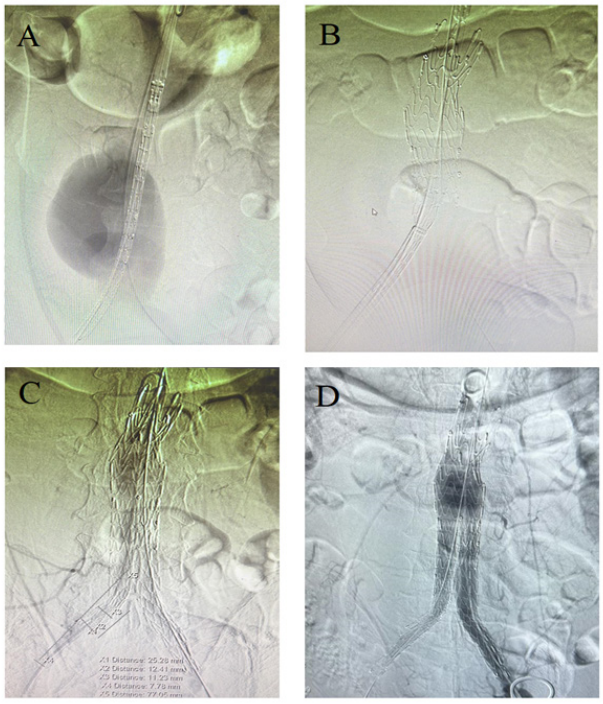

Figure 1. Imaging results of a patient's abdominal aortic aneurysm: (A) Filling of the aneurysm sac before the graft is opened during the EVAR procedure, (B) The main body of the EVAR graft placed at the infrarenal level, (C) Placement of the contralateral limb of the graft, and (D) The final configuration with the entire graft in place.

During the early hospitalization period of patients, renal functions and lower extremity arterial circulation were monitored. Post-discharge, patients were evaluated using abdominal CT or ultrasonography at the end of the first, 6th, and 12th months. In the control medical evaluations, the migration of the stent, the presence of endoleaks, and the stent's positional integrity were assessed.

The hospital's electronic information system and patient files were used to gather demographic and clinical data. During the 1-year follow-up period for the patients, data on early-phase outcomes, lengths of stays in ICU and the hospital, and post-procedure complications were collected.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Based on the results of the Kolmogorov-Smirnov test, normally distributed numerical data were presented as mean ± standard deviation and non-normally distributed variables were presented as median values (25th-75th quartiles; IQR). Categorical variables were expressed as numbers and percentages.

Results

In 5 of the patients who underwent EVAR, both iliac artery aneurysm and AAA were present, while in 28, only AAA existed. Three patients underwent the procedure on an emergency due to an aneurysm rupture, while 30 patients had it done under elective conditions. All patients treated in emergency situations received aorto-uniiliac stent grafts. Table 1 presents the pre-procedural characteristics and accompanying diagnoses. The demographic and clinical findings of the patients are presented in Table 1. The preoperative and postoperative levels of creatinine, blood urea nitrogen, and estimated glomerular filtration rate for the patients are shown in Table 2. No patients were detected with contrast-induced nephropathy or kidney damage.

The mean operation time was 2.5 (IQR: 2.0 – 3.5) hours and the mean fluoroscopy time was 40 (IQR: 24 – 65 minutes) minutes. The median length of ICU stay was 13 (IQR: 7-19) hr, and the median length of hospital stay was 3 (IQR: 1-7) days. During the follow-up period, complications were detected in seven patients (21.2%). One patient with a Type I endoleak underwent balloon dilation. In two patients with a Type II endoleak, the leak resolved without intervention. In one patient, a Type III endoleak developed due to stent migration, and an additional iliac artery stent graft was placed inside the existing stent (Table 3). In every patient with an endoleak, the proximal neck diameter and the aneurysm diameter exceeded the mean values, registering at >29 mm and >66 mm respectively. In one patient, despite the absence of an endoleak during follow-up examinations, lower extremity ischemia developed due to an occlusion in the graft leg. Consequently, a cross-femoral bypass was performed for this patient. In one patient without endoleak during the follow-up examinations, a rupture developed at the end of the one-year follow-up, and a femorofemoral crossover bypass was performed during the aorto-uni-iliac graft procedure for this patient. In one diabetic patient, healing problems in the femoral incision line were observed due to delayed scar tissue formation. There were no mortality cases during the early follow-up period (Table 3).

Table 1. Demographic and clinical findings in patients with abdominal aortic aneurysm.

Variables	All population n = 33
Demographic findings	
Gender, n (%)	
Male	28 (84.8)
Female	5 (15.2)
Age, years	72.4 ± 10.3
Smoking, n (%)	18 (54.5)
Comorbidities, n (%)	
Hypertension	30 (90.9)
Coronary artery disease	24 (72.7)
Diabetes mellitus	11 (33.3)
Peripheral artery disease	10 (30.3)
Chronic obstructive pulmonary disease	6 (18.2)
Chronic kidney disease	4 (12.1)
Symptomatic, n (%)	3 (9.1)
Morphological features	
Aneurysm diameter, mm	65.5 ± 12.4
Aneurysm length, mm	95.6 ± 20.8
Proximal neck length, mm	26.2 ± 5.1
Proximal neck diameter, mm	28.9 ± 4.5

Values are shown as mean±SD or median (IQR) or number (%).

Table 2. Postoperative findings in patients with abdominal aortic aneurysm.

Variables	All population n = 33
Endoleak, n (%)	
Type I	1 (3.0)
Type II	2 (6.1)
Type III	1 (3.0)
Peripheral vascular ischemia, n (%)	1 (3.0)
Stent migration, n (%)	1 (3.0)
Rupture, n (%)	1 (3.0)
Requirement for secondary intervention, n (%)	4 (12.1)
Occlusion in the graft leg, n (%)	1 (3.0)
Healing problem in femoral incision, n (%)	1 (3.0)
Length of ICU stay, hours	13 (7-19)
Length of hospital stay, days	3 (1-7)
Mortality, n (%)	-

Values are shown as mean±SD or median (IQR) or number (%). Abbreviations: ICU, intensive care unit

Table 3. Postoperative findings in patients with abdominal aortic aneurysm.

Variables	All population n = 33
Endoleak, n (%)	
Type I	1 (3.0)
Type II	2 (6.1)
Type III	1 (3.0)
Peripheral vascular ischemia, n (%)	1 (3.0)
Stent migration, n (%)	1 (3.0)
Rupture, n (%)	1 (3.0)
Requirement for secondary intervention, n (%)	4 (12.1)
Occlusion in the graft leg, n (%)	1 (3.0)
Healing problem in femoral incision, n (%)	1 (3.0)
Length of ICU stay, hours	13 (7-19)
Length of hospital stay, days	3 (1-7)
Mortality, n (%)	-

Values are shown as mean±SD or median (IQR) or number (%). Abbreviations: ICU, intensive care unit

Discussion

Advanced age, male gender, tobacco use, and the presence of additional diseases have been identified as the predominant risk factors for AAA.[8] In the management of AAA, EVAR presents as a superior alternative to conventional surgery, especially for elderly patients with elevated surgical risks and accompanying comorbidities.[5,9] Consistent with AAA risk factors, the mean age of patients who underwent EVAR was in the seventh decade. Predominantly male, these patients frequently had with comorbidities like hypertension and CAD. In this high-risk group, EVAR provides significant advantages such as eliminating the need for aortic clamping, reduced tissue trauma, feasibility under local or sedation anesthesia, shortened intensive care and hospital stay durations, and a diminished requirement for blood transfusions.[10] However, EVAR, compared to open surgery, has potential downsides such as a persistent risk of rupture, the likelihood of additional interventions, and a continual need for surveillance. The results from our single-center study indicate that a substantial fraction of patients are susceptible to complications during the early postoperative period.[11]

Endoleaks, which play a significant role in the progression of an aneurysm and carry a risk of rupture and mortality, are serious complications that require careful management. Previous studies have indicated endoleak incidences ranging from 4.1% to 26.4%.[12-14] In the current study, the endoleak rate was 12%, consistent with the literature. Type I endoleak, resulting from the graft's poor fit against the aorta, often requires stent adjustment through balloon dilation or an aortic extension.[10] It has been reported that Type 1 endoleak is responsible for 74% of all rupture cases after EVAR.[15] Hence, close monitoring of these cases after the procedure is paramount. In this study, one patient with a Type 1 endoleak underwent balloon dilation, and no rupture was observed over the course of one year. Type II endoleak, the most common leak type, arises following retrograde filling from the lumbar and mesenteric arteries. However, the endoleaks in these cases resolved over the course of the follow-up, consistent with previously reported studies.[12,16] Following EVAR, Type III endoleak, indicative of the aneurysm's inadequate defense against systemic pressure, emerges as a rare yet potentially fatal complication.[17] For a patient who developed a Type III endoleak, stent migration was identified as the cause. Stent migration can prompt the metal components to

interact with the fabric, thus making it a contributing factor to Type III endoleak.[18] The EUROSTAR registry has shown that patients with a late Type III endoleak are at a 9-fold higher risk of rupture compared to other types.[19] Eng et al.[20] previously reported that, for Type III endoleaks, endovascular intervention was applied in 68% of cases, open surgical repair in 10%, and hybrid procedures were chosen for 18%. When Type III endoleaks are identified early during completion angiography, immediate intervention is advised. This frequently involves redo ballooning at zones where components overlap or positioning an additional endograft to improve the overlap.[21] An additional iliac artery stent graft was placed in the patient who developed a Type III leak, and no rupture occurred during the one-year follow-up period.

A neck diameter exceeding 28 mm is identified as a risk factor for Type I endoleaks, while an enlarged aneurysm diameter presents a risk for Type III endoleaks.[22-24] In a previous study, a threshold value of >66 mm of aneurysm diameter was reported as predictive for a second EVAR intervention.[25] Both the aneurysm and neck diameters in patients with Type 1 and Type 3 endoleaks matched the descriptions provided above. On the other hand, in patients undergoing EVAR, the rate of secondary interventions stands at 12.1%, aligning with the 6-16% range highlighted in previous studies.[26,27] While endoleaks are frequently implicated in necessitating secondary interventions, other factors, notably rupture and peripheral vascular ischemia, can also mandate subsequent procedures.[28,29] However, over a one-year observation period post-EVAR, no mortality was observed among the entire cohort, encompassing those subjected to secondary interventions. Although the early postoperative survival rate was more favorable for EVAR than for open surgery, the findings from the EUROSTAR study indicated no marked distinction between the two procedures over a two-year observation period.[30] Similar results were also supported by several studies.[31-33]

This study has some significant limitations. It is primarily a retrospective analysis conducted at a single center. Additionally, long-term data for patients could not be obtained, as many patients continued their follow-ups at alternative centers. However, the primary objective of this study was to assess the early outcomes in patients who underwent EVAR. Lastly, the effectiveness of different graft brands could not be evaluated in this study.

Conclusion

EVAR, in older patients with coexisting comorbidities, offers advantages in diminishing durations in intensive care and hospital stays, potentially boosting early survival outcomes. However, it was determined that a significant portion of patients who underwent EVAR are at risk of complications even in the early stages. Hence, every patient treated with EVAR must be meticulously monitored, incorporating both the intraoperative completion arteriography and subsequent examinations.

ETHICAL DECLARATIONS

Ethics Approval: The study was performed in accordance with the Declaration of Helsinki, and was approved by the Bolu Abant Izzet Baysal University Clinical Resarches Ethics Committee (Date: 18.09.2023, Decision No: EA-1568)

Informed Consent: The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Conflicts of Interest Statement: The authors declare they have no conflicts of interest.

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

Availability of Data and Material: The data that support the findings of this study are availale on request from the corresponding author.

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

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CASE REPORT

Silent Pneumoperitoneum in a Major Burn Earthquake Survivor: Sigmoid Diverticular Perforation.

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Abstract

In February 2023, two major earthquakes with magnitudes of 7.6 and 7.8 occurred in Kahramanmaraş, Turkey. Major burns are traumas that involve a multisystemic organ response. Gastrointestinal complications, including stress ulcers and acute mesenteric ischemia-related conditions, are commonly seen in patients with major burns. While crush syndrome and extremity injuries are typically observed in earthquake survivors, burn cases have also been reported. However, hollow organ perforation due to blunt trauma from being trapped under the rubble is not commonly observed. In this case report, a patient who developed a scald burn during the earthquake, trapped under the rubble, and developed silent pneumoperitoneum on the 10th day after the earthquake is presented.

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Introduction

It is a well-known fact that major burn trauma triggers multiple organ hypoperfusion and can lead to ulcerations in the upper gastrointestinal system.[1] While sigmoid colon diverticula are present in the majority of adults, only about 4% of cases manifest as diverticulitis, abscess formation, or perforation.[2] Perforation of hollow organs is not commonly seen in blunt abdominal trauma cases.[3] This study presents a case of a patient who experienced a 15% total body surface area (TBSA) burn due to hot water spillage during the 2023 earthquake in Maraş, Turkey. The patient was rescued from the rubble after 25 hours and subsequently developed sigmoid diverticular perforation on the 14th day of treatment for the burn center.

Case

A 46-year-old female patient was rescued from the rubble approximately 25 hours after the 7.6 magnitude earthquake that occurred in Maraş, Turkey on February 6th. The patient suffered a 15% total body surface area (TBSA) third-degree burn, with 8% of the burn affecting the abdomen, as a result of hot water spillage during the earthquake. The patient was referred to our clinic on the 4th day after the trauma because of burns. Physical examination and radiological evaluations revealed no signs related to being trapped under the rubble. Fluid resuscitation was administered as maintenance treatment. Burn dressing was performed using silver sulfadiazine, and on the 3rd day of hospitalization, escharectomy was performed. On the 6th day of hospitalization, the patient developed elevated acute phase reactants, oliguria unresponsive to fluid replacement, and hypotension, suggesting sepsis. The patient was consulted with the infectious diseases department and started on antibiotic treatment. On the 10th day after the trauma, the patient complained of respiratory distress, and a chest X-ray revealed free air under the diaphragm (Figure 1). Contrast-enhanced abdominal CT scan showed perforation at the level of the sigmoid colon (Figure 2). Emergency laparotomy was performed, revealing diverticular perforation in the sigmoid colon (Figure 3). The abdomen was significantly contaminated. Sigmoid resection and end colostomy were performed. In the postoperative period, the patient required mechanical ventilator support and was extubated on the 4th day after the operation. 24 hours after extubation, the patient exhibited orientation and consciousness disturbances. On the 18th day of burn trauma and the 6th day of end colostomy, the patient underwent surgery for escharotomy and burn surgery. During the operation, a discharge was observed from the midline incision made for the laparotomy. Intraoperative assessment revealed evisceration. The patient died from intraabdominal sepsis on the 21st day following the trauma, which was the third day after the evisceration was discovered.

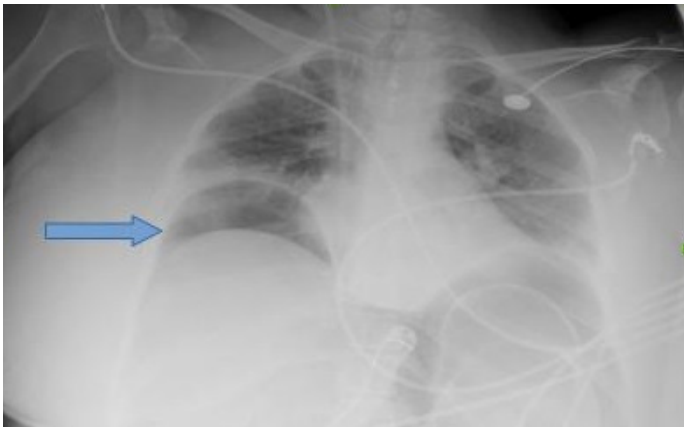

Figure 1

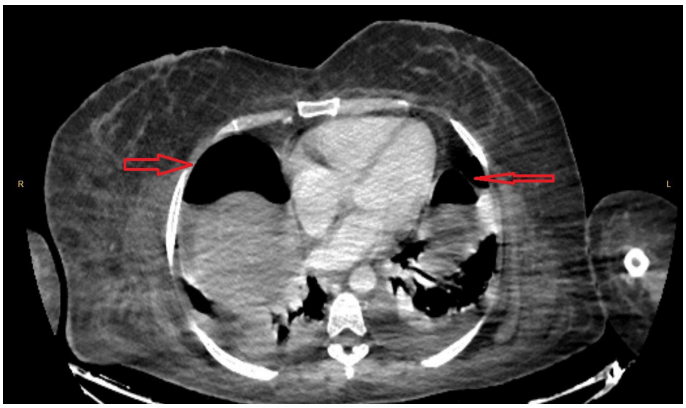

Figure 2

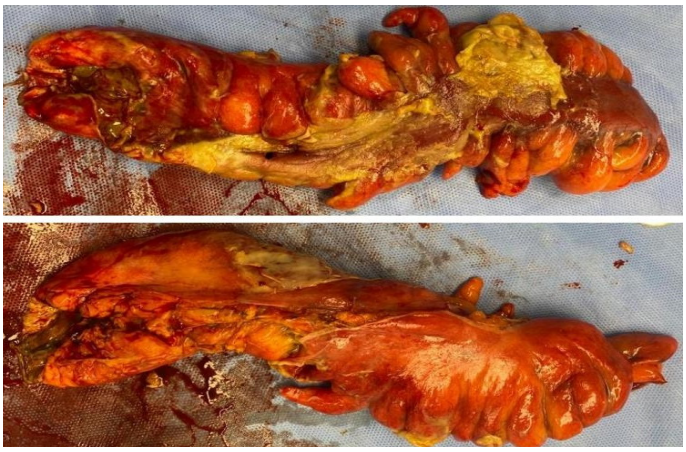

Figure 3

Discussion

On February 6, 2023, two earthquakes occurred in Maraş, Turkey, with magnitudes of 7.6 and 7.8, respectively, with an interval of 11 hours. These earthquakes resulted in the loss of over 50,000 lives. Many people were trapped under the rubble. Crush syndrome, blunt traumas, and extremity traumas were frequently encountered in earthquake victims who were rescued from the rubble. However, it was observed that hot liquid and contact burns also developed.

The patient in this case presentation had developed a 15% TBSA burn as a result of hot water spillage during the earthquake. On the 4th day after the earthquake, the patient was referred to our clinic due to the burn. Upon admission to our clinic, there were no additional injuries apart from the burn, despite being trapped under the rubble for 25 hours.

Full-thickness burns more than10% of the total body surface area are defined as major burns, which requries resuscitation.[4] The metabolic response to major burns is multisystemic.[4] In major burns, deaths due to burn shock occur within the first 72 hours, while deaths occure in the following weeks are often attributed to sepsis and multiorgan failure.[5]

Sigmoid diverticulosis is generally an asymptomatic condition. Rarely, pain in the lower left quadrant of the abdomen and an acute abdominal presentation may occur due to peritonitis. Diverticular perforation is the most serious and life-threatening complication of this disease.[6] When perforation occurs, symptoms such as fever, severe abdominal pain, and nausea are observed. However, in rare cases, silent pneumoperitoneum may develop, especially in older individuals, those using corticosteroids, or those using non-steroidal anti-inflammatory drugs (NSAIDs).[6] The presented patient has no history of using corticosteroids or NSAIDs.

Constipation, ileus, bleeding, pancreatitis, and ischemic bowel syndrome are some of the known gastrointestinal complications in burns patients.[7] Burns that cause stress gastroduodenal ulceration (Curling's ulcer) and perforation are well documented in the literature and are associated with significant morbidity and mortality.[7] Colonic ulcers and perforation appear to be uncommon in burns patients.[8,9]

In a review conducted by Fadel et al. in 2021, 9 studies reported colonic perforation at different levels.[7] Of those perforations four of them were sigmoid perforation. Three of them were reported by Cirodde et al in 2012 and all were diverticular perforation due to bowel obstruction which is well defined gastrointestinal complicaton of major burns.[1] The fourth sigmoid perforation is reported by Scaife et al which the perforation was due to intestinal obstruction associated with enteral feeding.[10]

The presented case in this study is, to the best of our knowledge, the fourth burn patient with sigmoid diverticular perforation reported in the literature. In this patient, silent pneumoperitoneum developed, and its etiology does not resemble the described known causes. The presented patient has not been entubated. Until the emergency laparotomy she was counsios and she had not any complaints or findings suggestive of intestinal obstruction or acute abdomen. Although the wounds were start to heal, all acute phase reactants were still elevated beside she presented oliguria unresponsive to fluid replacement, and hypotension. Patient had also respiratuary distress. Since the patient did not have any abdominal findings, GIS perforation might not have come to mind if free air under diaphragm was not seen in the chest X-ray. According to the peroperative findings, it was thougth that the perforation occured approximately 72 hours ago which corresponds to the time when acute phase reactants begins to elevated and renal function begins to decline.

Conclusion

Gastrointestinal complications are frequently observed in major burns and significantly impact morbidity and mortality.[7] While sepsis related to the burn is typically the first consideration in patients with resistant oliguria and/or anuria despite adequate and appropriate resuscitation, silent pneumoperitoneum should also be considered among the diagnoses in patients who show no improvement in acute phase reactants and lack sufficient urinary output despite appropriate antibiotic therapy.

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LETTER TO THE EDITOR

An Ounce of Prevention, a Pound of Passion: Unveiling Medical Students' Affinity for Family and Community Medicine in Spain

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We have read with both interest and surprise the study published by Akyon[1] et al. in this journal. Although the motivations of students seem to be aligned in Turkey, United States, Canada, and Germany; we firmly believe that the career choices of residents who opt for Family Medicine in Spain are driven by factors beyond personal reasons. In our country, the caregiver burden and job precarity in the public health sector are especially pronounced among professionals in this specialty.

As the authors acknowledge, every country has its unique circumstances. Unfortunately, the organization of primary healthcare centers in Spain often hampers young doctors from achieving schedules that allow them sufficient family time, thus complicating work-life balance, particularly with child rearing. The intense workload, coupled with the unpredictable hours, makes this a significant issue within the Family Medicine specialty in Spain. This concern is aligned with findings by Dyrbye et al.[2], who reported that poor work-life balance and burnout are common among physicians and may affect their specialty choice. Hence, the motivations of Family Medicine doctors correlate more with the discipline-related factors outlined in the article.

The vocation of service and the desire to make a positive impact on the lives of others are strong motivations for medical students choosing Family and Community Medicine.[3] Establishing long-term relationships with patients and their families allows for a more personalized and patient-centered approach. Medical students who aspire to make a difference in vulnerable communities are drawn to this specialty. Serving in underserved areas allows them to address healthcare disparities and contribute to improving the health outcomes of disadvantaged populations.

Family and Community Medicine offers a comprehensive approach to healthcare, covering all stages of life and focusing on disease prevention and health promotion. Medical students are attracted to the opportunity to provide care throughout the lifespan and play a role in preventive medicine.

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Contrary to common misconceptions, Family and Community Medicine encounters a wide range of pathologies and clinical cases. Medical students appreciate the diversity of situations encountered in primary care, which allows them to develop clinical and diagnostic skills across various medical areas. These factors reflect global trends as noted by Puertas et al,[4] who highlighted the universal importance of these factors in specialty choice.

Indeed, the influence of the educational environment cannot be underestimated in guiding the career trajectory of medical students. The pedagogical approach towards Family Medicine in Spain may not be optimally geared towards attracting young minds. As Bland et al.[5] have noted, the hidden curriculum in medical schools, marked by the values, norms, and practices that are transmitted to students in subtle, often unspoken ways, can significantly sway students' specialty preferences. Consequently, an enhanced emphasis on Family Medicine within medical curriculums might be a strategy worth considering to increase vocations in this specialty.

By promoting the unique aspects of this specialty, including its patient-centered approach, and comprehensive care, we can inspire more medical students to consider Family and Community Medicine as a fulfilling and impactful career choice.

Conflict of interest

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LETTER TO THE EDITOR

Influences on Family Medicine Career Choice: Implications for Healthcare Development

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Dear Editor,

We appreciate the thoughtful response "Unveiling Medical Students' Affinity for Family and Community Medicine in Spain" from our colleagues in Spain regarding our study.[1] We are grateful for the opportunity to engage in a constructive dialogue concerning the motivations and concerns that influence young doctors' decisions to pursue a career in Family Medicine. Understanding insights into the determinants that impact medical students' selection of family medicine holds paramount importance. We would like to address several key points raised in their letter.

Firstly, the authors rightly emphasize the impact of the local healthcare system and the organization of primary healthcare centers on young doctors' motivations. As Olid et al.[2] Have noted, most medical schools in Spain still lack mandatory core courses in family medicine similar to Turkiye, as demonstrated in our study. As highlighted by the authors, the impact of the educational environment and the hidden curriculum cannot be underestimated. To enhance the appeal of family medicine as a career choice, it is important to transform it into a respected academic discipline and elevate its standing and conditions within the healthcare system. We believe that there is a need for a new type of primary health care center that embraces everyone, touches each individual positively, has a biophilic structure design, is resistant to disasters, and prioritizes education and health. These new workplaces will also contribute to the prestige of family medicine in society and can be motivating for the employees and medical students who will prefer it.[3]

The diversity of clinical cases encountered in primary care is an important aspect that attracts medical students to this specialty. Family physicians act as gatekeepers, coordinating directions when necessary by providing a wide range of services including prevention, diagnosis, and treatment of common diseases. Moreover, family physicians utilize a holistic approach when treating patients and they are the most effective physician group in coordinating therapy, as they provide conti-

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nuous, longitudinal, and comprehensive medical care to the individual. On the other hand, the time constraint is one of the main problems in managing the therapy of patients for family physicians.[4]

Additionally, a strong referral system is vital for efficient healthcare and resource use in primary care. Without a clear referral process from primary to specialist care, patients can enter the healthcare system at any point they choose. Contrary to many European countries, Turkiye has not yet established a referral chain system. As the number of family physicians who have received specialization training in Turkiye increases, the quality of the service provided and the efficiency of implementing the referral chain will increase. The good functioning of the referral chain system may have many positive contributions to the health system, as well as significant negative effects such as an increase in the workload of primary care physicians. Technological tools can be developed as a solution to the clinician's time constraints, increased workload, and consequently increased preference by medical students. In the case of polypharmacy, fastrational.com can be given as an example of artificial intelligence-supported technological tools, which accelerates the detection of drug interaction with its bibliographies and enables the physician to fulfill the preventive medicine duty.[5]

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