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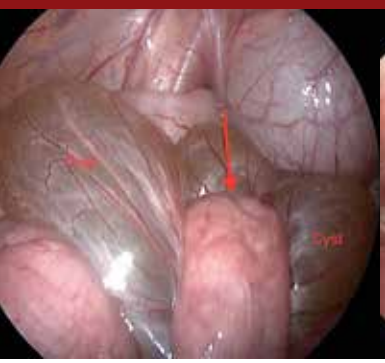
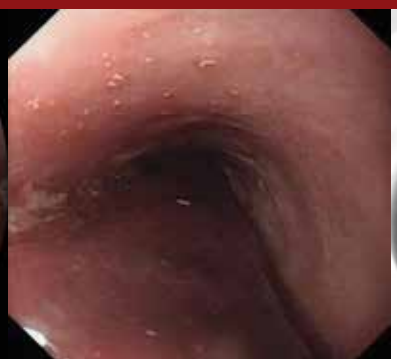
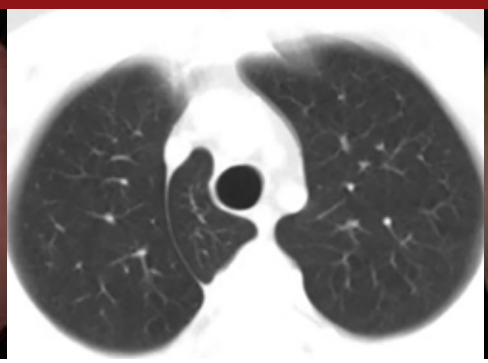
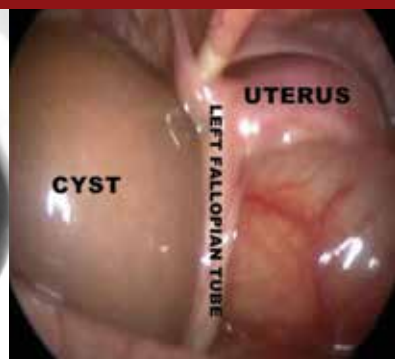

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The Cyprus Journal of Medical Sciences aims to publish manuscripts at the highest clinical and scientific level on all fields of medicine. The journal publishes original papers, review articles, case reports and letters.

Editorial and publication processes of the journal are shaped in accordance with the guidelines of the international organizations such as the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE).

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Contents

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Original Article

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Evaluation of the Glycemic Fluctuation as Defined as the Mean Amplitude of Glycemic Excursion in Hospitalized Patients with Type 2 Diabetes

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BACKGROUND
In addition to hemoglobin AIc (HbAIc), fasting plasma glucose (FPG), and postprandial glucose (PPG) levels, it is recommended to take glycemic variability into consideration for an assessment of the glycemic control of patients with type 2 diabetes. The mean amplitude of glycemic excursion (MAGE) is proposed to be a more sensitive method than HbAIc in evaluation of the glycemic variability. The objective of this study was to determine the MAGE levels of patients with type 2 diabetes who were hospitalized for poor glycemic control and to investigate whether these levels showed differences according to the diabetes duration and treatment characteristics.

MATERIAL and METHODS
This study included a total of 50 patients with type 2 diabetes (39 female, 11 male; mean age: 59.54±11.96; mean diabetes duration: 12.1 years) who were hospitalized at İstanbul Medeniyet University Department of Internal Medicine for glycemic control. Capillary venous blood samples were collected from the patients 10 times a day for 2 days and the MAGE levels were determined.

RESULTS
The MAGE, HbAIc, fasting plasma glucose, and postprandial glucose levels of the patients were 85.18±21.64 mg/dL, 10.71±2.40%, 196.70±61.25 mg/dL, and 240.02±79.51 mg/dL, respectively. MAGE levels were found to be 93.93±19.85 mg/dL in patients who use insulin, 82.94±21.41 mg/dL in those who use oral antidiabetics (OAD), and 74.37±19.75 mg/dL in patients who use both insulin and OAD. MAGE levels were higher in the insulin-using patients compared to those using insulin and OAD together (p=0.002).

CONCLUSION
It was observed in the present study that MAGE levels were higher in type 2 diabetic patients with impaired glycemic control.

Keywords: Type 2 diabetes, glycemic control, MAGE levels, treatment characteristic

INTRODUCTION

Glycemic variability is the variation of blood glucose between hypoglycemia and hyperglycemia during the day. A high variability leads to oxidative stress, which plays a role in the pathogenesis of vascular complications, ultimately resulting in endothelial damage (1, 2). Glycemic control of patients with type 2 diabetes (T2DM) is often assessed with hemoglobin AIc (HbAIc), fasting plasma glucose, and postprandial glucose. However, these three parameters do not always provide sufficient information about the glycemic variability (3-5). The mean amplitude of glycemic excursion (MAGE), glycoalbumin, and 1.5-anhydroglucitol measurements are usually used in evaluation of the glycemic variability (6-8). The MAGE level is calculated as the arithmetic mean of the elevations and reductions in blood glucose levels (9-11) and is reported to be a more sensitive method than HbAIc in evaluation of the glycemic variability (6, 12, 13).

The objective of this study was to determine the MAGE levels of patients with T2DM who were hospitalized for glycemic control and to investigate whether these levels showed differences regarding the diabetes duration and treatment characteristics and to evaluate their relationship with the clinical features.

MATERIALS and METHODS

Patients with T2DM who were hospitalized at İstanbul Medeniyet University Department of Internal Medicine were recruited. The exclusion criteria were: presence of severe renal, cardiac, and hepatic dysfunction; intensive care unit requirement (e.g., acute coronary syndrome, severe sepsis); diabetic decompensation (diabetic ketoacidosis, hyperglycemic hyperosmolar coma, lactic acidosis); and malignancy. The study was approved by the ethics committee of İstanbul Medeniyet University

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(blinded for peer review) (Date: 07/18/2014, No: 2014/0088) and written consents were received from the patients. The principles of the Helsinki Declaration were followed during the study.

Study Design: A detailed history was received from each of the patients, whereby age, gender, history, diabetes duration, treatment characteristics, smoking, alcohol consumption, and use of drugs were questioned. A physical examination was performed on patients who met the inclusion criteria and who agreed to participate in the study. In the physical examination, blood pressure, height, body weight, and waist circumference were measured by the same person using standard measuring instruments. Waist circumference was measured with the patients in a standing-up position with mild expiration, from the narrowest part of the waist at the plane that crosses between the spina iliaca anterior superior and arcus costa. Body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of the height in meters (kg/m^2). Capillary venous blood samples were collected from the patients 10 times a day for 2 days and the MAGE levels were determined. The calculated MAGE levels were compared according to diabetes duration and the treatment characteristics [insulin, oral antidiabetic (OAD), insulin+OAD].

Criteria of the American Diabetes Association were used for type 2 diabetes diagnosis (3). Glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride values were measured using the COBAS 8000 (Roche Diagnostics, Risch-Rotkreuz, Switzerland) auto-analyzer with the enzymatic method, while the HbAIc measure was carried out using the Primus Ultra 2 (Trinity Biotech, Jamestown, New York, USA) device with the boronate affinity HPLC method.

Mean Amplitude of Glycemic Excursion Measurements: Capillary venous blood samples were collected from the patients 10 times a day (at: 06.00, 08.00, 10.00, 12.00, 14.00 17.00, 19.00, 22.00, 24.00, and 03.00 hours) for 2 days. Blood glucose was measured using the Code free blood glucose measurement device (measures with electrochemical method used the Wide Gold Electrode technique). Standard deviation values were calculated using all the measurements for each patient. Each measurement value was subtracted from the previous one to calculate the difference (delta value). After absolute values of the delta were obtained, delta values smaller than the standard deviation were eliminated. The MAGE values were calculated by using the mean delta values that were greater than the standard deviation values (9).

Statistical Analysis: Number cruncher statistical system (NCSS) 2007 (NCSS, LCC, Kaysville, Utah, USA) and Power analysis and sample size (PASS) 2008 statistical software (NCSS, LCC, Utah, USA) were used for the statistical analysis. In addition to the descriptive statistical methods (the mean, standard deviation, median, frequency, percentage, minimum, and maximum), for comparison of the quantitative data, the Student t-test was used for comparisons between two groups of the variables with a normal distribution and the Mann–Whitney U test for comparisons between two groups of the variables with a non-normal comparison. The Kruskal–Wallis test was used for comparison between three or more groups with a non-normal distribution and the Mann–Whitney U test in the determination of the group causing the difference. Pearson correlation and Spearman correlation coefficients were used to evaluate the relationships between the variables. The significance level was set at $p<0.01$ and $p<0.05$ values.

TABLE 1. Treatment characteristics of the patients

			Total patients (n=50)
Oral antidiabetics (n, %)			25 (50.0)
Insulin (n, %)	Basal insulin	Glargine	33 (66.0)
		Detemir	10 (20.0)
	Bolus insulin	Aspart	30 (60.0)
		Lispro	2 (4.0)
		Glulisine	4 (8.0)
Oral antidiabetic+Insulin (n, %)			19 (38.0)
Antihypertensive (n, %)			33 (66.0)
Others (n, %)			38 (76.0)

TABLE 2. Demographic, anthropometric, and biochemical characteristic of the patients

	Total (n=50)	Female (n=39)	Male (n=11)	p
Age (year)	59.54±11.96	58.90±11.92	61.82±12.38	0.432
Smoking (n, %)	11 (22.0)	8 (20.5)	3 (27.2)	0.118
Alcohol (n, %)	2 (4.0)	0 (0.0)	2 (18.2)	0.008
Body mass index (kg/m2)	30.82±6.00	31.73±6.05	27.59±4.75	0.038
Waist circumference (cm)	105.56±15.86	107.05±16.20	100.27±14.02	0.271
Systolic blood pressure (mmHg)	131.82±16.95	133.10±16.00	127.27±20.17	0.397
Diastolic blood pressure (mmHg)	74.62±8.16	74.90±7.94	73.64±9.24	0.609
Fasting plasma glucose (mg/dL)	196.70±61.25	200.51±65.14	183.18±44.76	0.380
Postprandial plasma glucose (mg/dL)	240.02±79.51	242.44±76.48	231.45±93.02	0.779
HbAIc (%)	10.71±2.40	10.42±2.41	11.74±2.18	0.146
Total cholesterol (mg/dL)	222.86±96.08	224.13±101.51	218.36±77.81	0.972
HDL-cholesterol (mg/dL)	39.78±17.71	39.97±17.73	39.09±18.45	0.935
LDL-cholesterol (mg/dL)	121.05±40.27	120.52±39.58	122.80±44.66	0.863
Triglyceride (mg/dL)	274.76±239.20	269.33±183.29	294.00±390.09	0.287
ALT (IU/L)	28.96±32.66	26.54±33.24	37.55±30.43	0.108
Creatinine (mg/dL)	0.96±0.31	0.95±0.30	0.97±0.35	0.897
GFR (mL/dk)	91.87±38.42	88.76±35.47	102.90±47.7	0.433
MAGE (mg/dL)	85.18±21.64	83.38±20.75	91.56±24.48	0.297

HbAIc: hemoglobin AIc; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ALT: alanine aminotransferase; GFR: glomerular filtration rate; MAGE: mean amplitude of glycemic excursion

RESULTS

A total of 50 patients (39 female, 11 male; mean age: 59.54±11.96; min–max: 44–86) were included in the study. The mean diabetes duration was 12.1 years. Table 1 shows the treatment modalities of the patients.

The demographic, anthropometric, and biochemical characteristics of the patients are given in Table 2. The BMI score was

TABLE 3. Comparison of the MAGE levels according to the treatment characteristics of the patients

		MAGE (mg/dL)	HbAlc (%)	FPG (mg/dL)	PPG (mg/dL)
[1]Insulin		93.93±19.85	11.10±2.52	199.76±72.06	261.44±76.47
[2]OAD		82.94±21.41	9.12±2.94	177.83±54.02	195.67±56.68
[3]Insulin+OAD		74.37±19.75	10.69±1.93	198.63±48.40	225.84±83.77
	p	0.008	0.295	0.614	0.097
[a]Post-hoc	[1-2]p	0.291	-	-	0.067
	[1-3]p	0.002			0.115
	[2-3]p	0.514			0.437

MAGE: mean amplitude of glycemic excursion; HbAlc: hemoglobin Alc; OAD: oral antidiabetic; FPG: fasting plasma glucose; PPG: postprandial glucose

TABLE 4. Comparison of the MAGE levels according to the basal insulin types

	MAGE (mg/dL)
Glargine (n=33)	84.09±22.72
Detemir (n=10)	89.68±20.64
p	0.386

MAGE: mean amplitude of glycemic excursion

TABLE 5. Comparison of the MAGE levels according to the HbAlc values

	MAGE (mg/dL)	p
HbAlc: ≤8% (n=8)	75.49±26.25	
HbAlc: 8.1–10% (n=7)	82.98±18.00	0.432
HbAlc: ≥10% (n=35)	87.83±21.10	
HbAlc: <8% (n=8)	75.49±26.25	0.278
HbAlc: ≥8% (n=42)	87.03±20.49	

MAGE: mean amplitude of glycemic excursion; HbAlc: hemoglobin Alc

TABLE 6. Comparison of the MAGE levels according to diabetes duration of the patients

Diabetes duration (years)	n	MAGE (mg/dL)	p
0–5	12	86.83±14.93	0.775
6–10	11	75.96±20.19	
11–15	7	84.56±17.84	
16–20	9	95.24±27.70	
>20	11	84.76±25.45	

MAGE: mean amplitude of glycemic excursion

higher (p=0.038) and alcohol consumption was lower (p=0.008) in females than in males. MAGE values differed between 31.6 and 139.88 mg/dL with an average of 85.18±21.64 mg/dL. No statistically significant difference was found between the genders in terms of MAGE values (p>0.05). The overall average blood glucose level was found to be 211.88 mg/dL, with a standard deviation of 67.57 mg/dL.

Comparison of the MAGE, HbAlc, fasting blood glucose, and postprandial blood glucose values are given in Table 3. MAGE values were found to be higher in insulin users than in insulin+OAD users (93.93±19.85 mg/dL vs 74.37±19.75 mg/dL, p=0.002). No significant difference was found between insulin, OAD, or insulin+OAD users in terms of HbAlc, fasting plasma glucose, or postprandial plasma glucose. Although not statistically significant, HbAlc, fasting blood glucose, and postprandial blood glucose values were found to be higher in OAD users compared to insulin or insulin+OAD users.

The mean MAGE levels according to the basal insulin types used by patients are given in Table 4. The mean MAGE levels did not show a significant difference between insulin glargine and detemir users (84.09±22.72 mg/dL vs 89.68±20.64 mg/dL, p>0.05).

The mean MAGE levels of the patients according to the HbAlc values are given in Table 5. Although it did not reach statistical significance, the mean MAGE values were higher in patients with HbAlc ≥%8 compared to those with HbAlc <%8.

The mean MAGE levels according to diabetes duration are given in Table 6. No significant difference was found between the groups.

DISCUSSION

In the present study, MAGE levels were found to be higher in the group of patients hospitalized for glycemic control. MAGE levels were higher in insulin users than in insulin+OAD users but these levels did not show significant differences in terms of diabetes duration and basal insulin use.

HblAc reflects the average glycaemia in diabetic patients; however, it is insufficient to show the glycemic variability (10, 11). Therefore, today, various methods showing glycemic variability are used for the follow-up of diabetes control and in order to predict possible complications. Increased glycemic fluctuations have been demonstrated to cause more severe endothelial damage and oxidative stress, resulting in serious cardiovascular complications, compared to constantly high blood glucose levels (12, 14-16). Today, the methods used in evaluation of the glycemic variability are MAGE, 1.5- anhydroglucitol and fructosamine (7, 17-19). MAGE, which is based on close monitoring of the blood glucose variabilities, is an important parameter in providing glycemic control and for the prediction of possible complications (9, 20). However, the reference values to be used for MAGE represent a controversial issue. In a study by Zhou et al. (21), conducted in order to define reference values of MAGE, continuous glucose monitoring measures were carried out in 434 non-diabetic healthy persons for 72 h. The upper limit of MAGE was found as 70.2 mg/dL with a standard deviation (ss) of 25.2 mg/dL for healthy persons. In a study by Hill et al. (13) with different ethnic groups, MAGE values were calculated with continuous glucose monitoring of 70 non-diabetic persons for 72 h and the normal range was found as 0.0–50.4 mg/dL. Whereas in our study, the MAGE values of our patients differed between 31.6 and 139.88 mg/dL and the average value was found to be 85.18 mg/dL with a SD of 21.64 mg/dL, thus the average MAGE value calculated in our study is higher than the reference values calculated in other studies. This finding supports that MAGE may be higher in pa-

tients with type 2 diabetes with impaired glycemic control. Also, in our study MAGE levels increased as HbIAc values increased, suggesting that MAGE can be a reliable indicator for poor glycemic control.

It is known that diabetes treatments have different effects on MAGE. In a study evaluating the glycemic variability and relationship of this variability with cardio metabolic parameters and antidiabetic treatments in type 2 diabetics, MAGE values were found to be significantly higher in insulin users compared to in patients who used oral diabetics or who received diet therapy alone (4). In a study by Shimoda et al. (22), the MAGE values of 40 diabetic patients who used multiple doses of insulin therapy were evaluated with 1-day SMBG measures carried out 6 times a day, and a significant reduction was observed in MAGE values that were evaluated 12 weeks after sitagliptin was added to the treatment. In a study by Su et al. (23), acarbose was added for 2 weeks to the treatment in 45 of 86 type 2 diabetic patients who used mix analog insulin and who had a MAGE value ≥61.2 mg/dL, while the remaining 41 patients continued to use a mixed analog insulin therapy. In that study, a significant reduction by 40% was observed in the MAGE values of the group with acarbose compared to the values measured 2 weeks previously. Whereas in the present study, the MAGE values of the patients who used insulin alone were found to be significantly higher compared to the patients who used insulin and OAD in combination. This finding might have resulted due to the fact that the insulin group consisted of patients who already had poor glucose control.

There are studies investigating the effect of different insulin treatments on MAGE. In a study by Service et al. (9) investigating whether moderate acting insulin therapy and short-acting insulin therapy have any difference in the glycemic variability, no difference between the regimens was found, although the incidence of hypoglycemia was higher with the short-acting insulin.

Limitations: The most important limitation of this study is the lack of blood glucose measurements with continuous glucose monitoring to determine the MAGE values. Furthermore, it may be considered an imperfection that the 1.5-anhydroglucitol and fructosamine values were not studied.

CONCLUSION

High MAGE levels observed in poor controlled type 2 diabetic patients hospitalized for glycemic control support that MAGE may be a good marker for the evaluation and follow-up of glycemic control.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Medeniyet University (Date: 07/18/2014, No: 2014/0088).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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Original Article

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Predictive Value of Fragmented QRS in Response to Levosimendan Therapy in Patients with Heart Failure

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BACKGROUND
Data on the effect on re-hospitalization are limited when levosimendan is added to conventional treatment. We aimed to investigate the role of fragmented QRS (f QRS) on the surface electrocardiogram in predicting the response to levosimendan therapy in patients with acute systolic heart failure.

MATERIAL and METHODS
Patients with a left ventricular ejection fraction of <35% were enrolled in this retrospective observational study. They were administered a levosimendan therapy for 24 h, and the number of re-admissions due to decompensated heart failure annually were recorded. Patients were divided two groups: group I, 0-7 admissions per year and group 2, >7 admissions per year.

RESULTS
There were 42 patients in group I and 24 in group 2. The presence of fragmented QRS was seen in 41% of the patients in group I and in 92% of the patients in group 2 (p<0.001). The presence of fragmented QRS during the hospitalization of patients treated with levosimendan was found to be an independent predictor of the admission of more than 7 patients in the multivariate analysis.

CONCLUSION
The presence of fragmented QRS during hospitalization may predict a lower response to levosimendan therapy in patients with decompensated heart failure.

Key words: Heart failure, electrical heterogeneity, levosimendan

INTRODUCTION

Positive inotropic drugs are necessary in patients with acute decompensated heart failure and systolic dysfunction and having hypotension and/or peripheral hypoperfusion despite vasodilator and diuretic therapy (1). Levosimendan is dissimilar from other positive inotropic remedies in terms of providing increased contractility without enhancing the oxygen consumption of the heart (2). It increases cardiac contractility as a means of enhancing the calcium sensitivity of contractile proteins in the myocardium. Furthermore, it leads to the opening of adenosine triphosphate-sensitive potassium channels in vascular tissues and vasodilatation (3).

The survival benefit of levosimendan is unclear; however, clinical improvement has been demonstrated in various trials. This condition may be due to the heterogeneity of the patient populations in these studies. There are trials specifying patient groups that might further benefit from levosimendan. QRS duration and brain natriuretic peptide (BNP) change have been found to be important for evaluating the response to levosimendan therapy (4, 5). We analyzed patients applying to a hospital with acute decompensated heart failure and who stabilized and were discharged following medical treatment including levosimendan infusion. Parameters affecting annual admission numbers by virtue of decompensated heart failure were investigated. Thus, in our trial, we intended to predict which patients will further benefit from levosimendan therapy.

MATERIAL and METHODS

Study Population

Sixty-six patients under clinical follow-up between 2011 and 2016 were enrolled in this retrospective study; these patients were hospitalized due to acute decompensated heart failure and were administered levosimendan due to the requirement of intravenous inotropic support despite optimal medical therapy.

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Exclusion criteria included permanent atrial fibrillation (AF), paroxysmal AF, systolic blood pressure persistently lower than 85 mmHg or heart rate persistently at 115/min or higher, aortic or mitral valve stenosis, hypertrophic or restrictive cardiomyopathy, second- or third-degree atrioventricular block, severe hepatic dysfunction (liver enzyme levels two times higher than the normal levels), serum creatinine levels higher than 2.5 mg/dL, recent myocardial infarction (within 8 weeks), utilization of an another inotropic drug in the same hospitalization, history of cardiac pacemakers, and sustained or non-sustained ventricular tachycardia. Ethics committee approval and informed consent was obtained.

Study Protocol

Hospitalization data were assessed, where patients were medicated with levosimendan as well as vasodilators and diuretics. All patients received levosimendan with a loading dose of 12 mcg/kg/min over 10 min, followed by an infusion of 0.1 mcg/kg/min for 24 h. The total hospitalization duration was calculated. Moreover, the mean furosemide dose per day was determined. Patients' outpatient follow-up registries were searched in detail. Furthermore, the first re-admission duration and annual admission number due to acute decompensated heart failure despite regular and optimal medical therapy were registered. Patients were divided two groups: group 1, 0-7 admissions per year and group 2, >7 admissions per year. Factors affecting the first admission duration and annual hospitalization rate were investigated.

Patients' electrocardiograms (ECGs) were evaluated prior to initiating levosimendan therapy. The presence of fragmented QRS (fQRS) was investigated in patients'12-lead surface ECGs (Nihon Kohden-Cardiofax S ECG, Japan; 1250 K, 0.5 Hz to 150 Hz filter range, 60 Hz AC filter, 25 mm/s,10 mm/mV) prior to levosimendan infusion. The definition of fQRS was QRS complexes with the presence of an additional R wave or S wave or the presence of <1 R' (fragmentation) in two contiguous leads, corresponding to a major coronary territory [inferior (D2, D3, aVF), lateral (DI, aVL, V6), or anterior (V1-V5) derivations] (6). Additionally, for QRS complexes of a typical right bundle branch block (≥120ms) or left bundle branch block (LBBB; ≥120 ms), fQRS was defined as a QRS complex with >2 R' waves or notches in the R or S waves in two contiguous leads (7).

The relationship between fQRS presence and the annual admission rate and total weight loss was determined. Blood pressure and heart rate on admission were recorded. Transthoracic echocardiography (EPIQ 7 Ultrasound System, PHILIPS, HEIDE, The Netherlands) registries of LVEF, heart chamber diameters, and valvular pathologies were reviewed according to the recommendations of the American Echocardiography Association. Hemogram and biochemistry parameters were noted.

Statistical Analysis

Data were analyzed with Statistical Package for the Social Sciences version 15.0 for Windows (SPSS Inc.; IBM, Los Angeles, USA). Categorical variables were presented as frequency and percentage. The chi-square test and Fisher's exact test were used to compare categorical variables. The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Student's t-test was used for variables with normal distribution, and the values were presented as mean±SD. Continuous variables without normal distribution were analyzed using the Mann–Whitney U test and the values are presented as median values (50th persentile) and interquartile ranges (25th and 75th). One-way analysis of variance and the Kruskal-Wallis test were respectively used for parametric and non-parametric variables to compare tertiles. Multivariate logistic regression analysis was used to evaluate the independent associates of the risk of increased re-hospitalization rate. Parameters with a p-value of less than 0.1 in the univariate analysis were included in the model. Odds ratios and 95% confidence intervals were calculated. A two-tailed p-value of <0.05 was considered to be statistically significant.

RESULTS

Sixty-six patients, 54 of whom were males, were included. Forty-two patients were in group 1 and 24 were in group 2. Thirty percent of the patients applied to the hospital in the first month, 55% applied within 2 months, and 92% applied within 6 months because of acute decompensated heart failure. Demographic and clinical characteristics of the patients according to the number of annual applications are listed in Table 1.

The presence of fQRS was found in 41% of the patients in group 1 and in 92% of the patents in group 2 (p<0.001) (Table 2).

Univariate and multivariate logistic regression analyses was performed for factors affecting the number of annual applications. The presence of fQRS during the hospitalization of patients treated with levosimendan was found to be an independent predictor of the admission of more than 7 patients in the multivariate analysis. There was a highly positive significant correlation between the presence of fQRS and re-admission (r=0.555, p<0.001) (Table 3).

DISCUSSION

In our trial, patients with fQRS on their ECGs had more re-admissions to the hospital than those without fQRS on their ECGs, irrespective of the LVEF. This finding may be a subsidiary parameter to the presence of fQRS on ECGs to predict the response to levosimendan therapy in patients with heart failure.

Acute decompensated heart failure is a considerable cause of morbidity and mortality. Such patients are generally treated with diuretics and vasodilators. Positive inotropic drugs are added to the conventional treatment when peripheral hypoperfusion signs are present. Levosimendan does not distinctively potentiate intracellular cyclic adenosine monophosphate and calcium levels; in contrast to other inotropic drugs, levosimendan stabilizes cross-bonds between actin and myosin, leading to enhanced contractility (8-10). Levosimendan stimulates adenosine triphosphate-sensitive potassium channels on vascular smooth muscles, resulting in arterial and venous vasodilatation. Thus, it reduces the preload and afterload (11). Besides these, levosimendan enhances coronary vasodilatation via the nitric oxide-dependent pathway, which inhibits phosphodiesterase-3 and contributes to the protection of the myocardium from ischemia by means of increasing the coronary blood flow (12, 13). It has been demonstrated that levosimendan improves the myocardial systolic function in patients with a stunned myocardium who underwent percutaneous coronary intervention due to acute myocardial infarction (14).

TABLE 1. Patient characteristics according to annual admission number due to decompensated heart failure (which show a normal distribution mean ± SD, not show a normal distribution median (25^{th} vs. 75^{th} percentile)

Variable	0-7 admissions (n=42)	8≤ admissions (n=24)	P value
Age, years	64.5 ±11.9	64.9±15.0	0.626
Male gender, n(%)	34 (81%)	20 (83%)	0.809
Annual readmissions	3.8±1.6	9.5±1.3	<0.001
Systolic BP, mmHg	101±9	102±14	0.859
Diastolic BP, mmHg	63±16	65±10	0.565
Heart rate, beat/min	86±8	90±9	0.101
Serum creatinine	1.2±0.5	1.4± 0.5	0.179
LVEF,%	28.1±7.1	25.6±9.0	0.221
LVEDD, mm	62.6±6.5	65.4±10.0	0.181
LVESD, mm	48.7±8.1	50.8±11.5	0.382
LA diameter, mm	49.0±7.3	51.4±6.4	0.180
DM, n(%)	11 (26%)	10 (42%)	0.194
HT, n(%)	27 (64%)	16 (67%)	0.845
Ischemic cardiomyopathy, n(%)	32 (76%)	17 (71%)	0.632
NYHA functional class 3, n(%)	36 (86%)	6 (14%)	14 (58%)
NYHA functional class 4, n(%)	10 (42%)	0.013	
Mean duration of hospitalization, day	6.7 ± 1.3	7.4 ± 2.0	0.068
History of CABG, n(%)	8 (19%)	3 (13%)	0.492
Mean furosemide dose, mg/day	65±11	77±16	0.001
BB usage, n(%)	30 (71%)	20 (83%)	0.278
ACEI usage, n(%)	30 (71%)	19 (79%)	0.489
ARB usage, n(%)	5 (12%)	1 (4%)	0.293
Spironolactone usage, n(%)	23 (55%)	19 (79%)	0.047
Digoxin usage, n(%)	17 (41%)	11 (46%)	0.672

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta blocker; BP: blood pressure; CABG: coronary artery bypass grafting; DM: diabetes mellitus; HT: hypertension; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MPV: mean platelet volume; NYHA: New York Heart Association

TABLE 2. Electrocardiographic characteristics of the groups according to the annual admissions

Variable	0-7 admissions (n=42)	8≤ admissions (n=24)	P value
Presence of LBBB, n(%)	2 (4.8%)	4 (17%)	0.106
Presence of fQRS, n(%)	17 (40.5%)	22 (91.7%)	<0.001
Localization of fQRS, %			
anterior lead	14.3 %	20.8 %	0.001
inferior lead	21.4 %	50.0 %	
lateral lead	4.8 %	20.8 %	

LBBB: left bundle branch block; fQRS: fragmented QRS

TABLE 3. Evaluation of the factors affecting the annual re-admissions>7 by univariate and multivariate logistic regression analysis

	Univariate		Multivariate	
Variable	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (years)	1.002 (0.964-1.042)	0.906		
LV diameter (/1mm)	3.000 (0.591-15.226)	0.185		
LA diameter (/1mm)	1.051 (0.976-1.131)	0.110		
fQRS	16.176 (3.355-78.004)	0.001	10.501(1.534 -71.903)	0.017
LBBB	4.000 (0.674-23.725)	0.127		
DM	2.013 (0.695-5.832)	0.197		
HT	1.111 (0.386-3.200)	0.845		
ARB	0.322 (0.035-2.931)	0.314		
LVEF	0.959 (0.898-1.025)	0.220		
Sprinolactone	3.139 (0.987-9.988)	0.053	3.284(0.747-14.439)	0.116
Beta Blocker	2.000 (0.564-7.087)	0.283		
Digoxin	1.244 (0.452-3.424)	0.672		
Furosemide dose	1.071 (1.021-1.123)	0.005	1.017(0.960-1.077)	0.573
Serum creatinine	1.942(0.718-5.257)	0.191		
Heart rate	1.054 (0.988-1.124)	0.108		

ARB: angiotensin receptor blocker; DM: diabetes mellitus; HT: hypertension; fQRS: fragmented QRS; LA: left atrium; LBBB: left bundle branch block; LV: left ventricle; LVEF: left ventricular ejection fraction

Levosimendan also has neurohormonal effects. Thirty to sixty percent reduction of BNP and N terminal-BNP levels has been reported after levosimendan infusion (15). Additionally, it has been stated that levosimendan diminishes the levels of proinflammatory cytokines and apoptosis mediators such as endothelin I, interleukin 6, and tumor necrosis factor-alpha (16-18). It has been demonstrated that this neurohormonal influence continues for at least 7 days (16-18). The prolonged impact of levosimendan may be related to its active metabolite OR-1896, which has an extended half-life of 70-80 h despite the short half-life of 1 h for levosimendan.

Six-month all-cause mortality or re-hospitalization for heart failure significantly decreased in patients with a 58% or more reduction in BNP levels following levosimendan therapy in a study by Farmakis et al. (5) that was performed to predict the response to levosimendan therapy. Another study that searched for the significance of cardiac rhythm to the response to levosimendan therapy showed no difference between the sinus rhythm and AF in terms of the effect on left ventricular systolic and diastolic functions (19). Patients with a basal QRS duration lower than 120 msn had a better outcome in short-term levosimendan therapy in a trial evaluating echocardiographic parameters.

It has been demonstrated in a study assessing ischemic and non-ischemic heart failure patients with an LVEF of <35% that the presence of fQRS on ECGs is correlated with the increased re-hospitalization due to decompensated heart failure and cardiovascular mortality (20). In a trial evaluating patients with post-myocardial infarction heart failure, the presence of fQRS was related to higher cardiac death and hospitalization rates due to heart failure (21). fQRS is more sensitive than the Q wave

in demonstrating myocardial scar tissue in a study by Das et al. (6, 7) fQRS denotes an impairment in signal conduction by virtue of myocardial scarring, fibrosis, and ischemia. In our trial, earlier re-admissions and increased annual re-admissions after levosimendan therapy in patients with fQRS on ECGs may result from a decreased contractile reserve on account of myocardial fibrosis and scarring. This may be a subsidiary parameter to predict a poorer response to levosimendan therapy.

Study Limitations

The number of patients in our trial is insufficient, and the number of patients with non-ischemic dilated cardiomyopathy is particularly insufficient. In our study population, due to the weight of the males, the results may not reflect the findings in females. Moreover, patients with permanent AF and documented paroxysmal AF were not included. However, there is no Holter ECG recording in all patients, and there may be undetectable paroxysmal AF episodes. Furthermore, we could not acquire body mass indexes due to the fact that they were not recorded and our trial is not prospective.

CONCLUSION

The evaluation of the presence of fQRS on ECGs may provide substantial information in patients with decompensated heart failure. The presence of fQRS on ECGs might assist in predicting more frequent re-admissions in patients with heart failure treated with levosimendan.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Antalya Training and Research Hospital (2014).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Original Article

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The Existence of Continuous Systemic Inflammation in Pregnant Women with Hyperemesis Gravidarum

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BACKGROUND
To evaluate the serum inflammatory markers in the first trimester in which hyperemesis gravidarum (HG) usually occurs and in the late second trimester when symptoms of HG usually resolve.

MATERIALS and METHODS
The study population consisted of 170 pregnant women with HG and 185 healthy gestational-age-matched controls. White blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) were compared during the first and the late second trimester.

RESULTS
In the first trimester, WBC (9.25 (2.90)×10^3/μl vs. 8.25 (2.35)×10^3/μl, p=0.001), NLR (4.54 (2.86) vs. 3.66 (1.25), p=0.021), and PLR (155.79 (69.33) vs. 128.75 (50.09), p=0.001) for the HG and control groups, respectively. In the late second trimester, WBC (11.31 (2.31)×10^3/μl vs. 10.03 (3.67)×10^3/μl, p=0.001), NLR (4.89 (1.58) vs. 4.05 (1.45), p= 0.01), and PLR (135.28 (61.41) vs. 119.10 (55.66), p=0.032) for the HG and control groups, respectively.

CONCLUSION
HG may be related to subclinical systemic inflammation that persists even after complete recovery.

Keywords: Hyperemesis gravidarum, nausea, vomiting, inflammation, etiology

INTRODUCTION

Nausea and vomiting are the most common complaints of pregnant women in the first trimester, affecting 70%-80% of all pregnancies (1). These mild symptoms are usually described as morning sickness (2) because nausea and vomiting typically occur in the morning and resolve during the day time. Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting during pregnancy (3) that leads to weight loss, dehydration, electrolyte and acid-base imbalances, ketonuria, and nutritional deficiency (4). It affects 0.8%-3.2% of pregnant women (5, 6).

Although the etiology of the disease remains ambiguous, many theories, such as hormonal changes, abnormal gastrointestinal motility, Helicobacter pylori levels, nutrient deficiencies, abnormalities in carbohydrate metabolism, endocrine disorders, alterations in lipid levels, changes in the autonomic nervous system, genetic factors, and immunologic dysregulation, have been suggested (7-10). However, none of these explanations have convincingly enlightened the etiopathogenesis of HG thus far. Since the exact etiology remains unknown, the current treatment of HG becomes empirical and is insufficient.

Inflammation is regarded to play an important role in HG pathogenesis (11). Recent studies have demonstrated that pregnant women with HG have higher inflammatory markers when compared to healthy pregnant women without HG in the first trimester. Measuring white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and red blood cell distribution width (RDW) is an inexpensive and convenient way to identify systemic inflammation in the body (12-15). Studies have shown that NLR, PLR, and RDW values are highly associated with the prognosis of diseases related to inflammation (16-19). The studies investigating the relationship between inflammation and HG are primarily focused on the inflammatory markers in the first trimester as HG predominantly occurs in this period (20, 21). However, it is unclear whether the high inflammatory markers in patients with HG cause the disease or they are the product of HG. Assuming that systemic inflammation plays an important role in the etiopathogenesis of HG, we hypothesize that if the inflammation is the culprit in the development or exacerbation of the disease, it should exist throughout the pregnancy, or at least inflammatory abnormalities should be detectable during the period where HG completely heals and even after the symptoms of the disease cease. In this current study, we aimed to evaluate the serum inflammatory markers in the

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first trimester, in which HG usually occurs, and in the late second trimester when symptoms of HG have completely resolved.

MATERIALS and METHODS

This study was carried out as a comparative study between December 2012 and March 2015. The study complies with the Declaration of Helsinki and the study protocol was approved by the local ethical committee. Informed consent was obtained from participants according to the tenets of the Declaration of Helsinki. The study group consisted of 170 pregnant women who were hospitalized due to severe nausea and vomiting and diagnosed with HG, and the control group was selected from a population of 185 healthy gestational-age-matched pregnant women who visited our prenatal clinic regularly. HG was defined as obstinate nausea and vomiting and positive ketonuria (at least 2+) on a urinary dipstick test without any detectable cause. Exclusion criteria for all participants were the existence of any type of disease related to inflammation such as hepatic, renal, or thyroid diseases, systemic or infectious diseases, gestational trophoblastic disease, gestational diabetes mellitus, gastrointestinal disorders, metabolic disorders, collagen vascular diseases, smoking habits, alcohol consumption, urinary tract infection, and pregnancy with multiplets. Patient characteristics, such as age, gravity, parity, and gestational age were recorded. The gestational age was determined based on the last menstrual period and/or ultrasound findings during early pregnancy. For the study group, blood samples for measurement of serum inflammatory markers and urine samples for determining the urine ketone levels were obtained from patients with HG prior to intravenous hydration treatment in their first trimester. For the control group, all samples were collected during their prenatal visit in the first trimester.

Blood samples were collected in EDTA-containing tubes and processed in a Sysmex XE 2100 device (Roche Diagnostics, Basel, Switzerland) for complete blood cell count (CBC) analysis. CBC parameters (WBC, neutrophil, lymphocyte, hemoglobin, hematocrit, RDW, and platelet counts) and urine ketone levels of the patients were measured. All subjects in the study were advised to have prenatal appointments in their late second trimester (between 24 and 28 gestational weeks) in order to re-evaluate their serum inflammatory markers and urine samples. This period is usually the most comfortable time of the pregnancy because most of the early pregnancy symptoms, such as nausea and vomiting, gradually diminish and also pregnant women may have a glucose screening test called the glucose challenge test (GCT) in this period. While pregnant women received the GCT, they were simultaneously tested for inflammation markers in the blood. Subjects were questioned regarding the presence of nausea, vomiting, and experiences of any symptom related to bodily infections. The exclusion criteria mentioned above were applied to all participating pregnant women in their late second trimester as well. Patients diagnosed with gestational diabetes were also excluded from the study due to concerns related to inflammation. Statistical analyses were performed using the Statistical Package for the Social Sciences version 21 (SPSS Inc., Chicago, IL). Continuous variables were inspected for normality using the Shapiro–Wilk test. Data were reported as mean ±SD or median with interquartile ranges as appropriate. The Mann–Whitney U test was used for the variables without normal distribution, and the Student's T test was used to evaluate statistically significant differences between normally distributed variables. The two-way repeated ANOVA was used to evaluate group, time, and group×time interaction effects on clinical variables, and the Wilcoxon-signed rank test was used to compare the first and late second trimester blood values. A p value less than 0.05 was considered statistically significant. A post hoc power calculation was performed to test whether the sample size was sufficient to adequately detect significant differences between groups. For this purpose, the G*Power Ver.3.1.9.2 (Franz Faul, Universitat Kiel, Germany) computer program was used. Assuming an alpha of 0.05, effect size of 0.39, and a sample size of 170 for each group, the power was calculated to 95%.

TABLE 1. The demographic properties and urine ketone values of the groups

	HG (n=170)	Controls (n=185)	p
Age (year)	27.42±5.03	26.54±6.9	0.173
Gravidity	2(1)	2(2)	0.312
Parity	0(1)	1(1)	0.078
Abortion	0(0)	0(0)	0.123
Gestational weeks in the first trimester	9.2(3.9)	9.05(3.4)	0.163
Gestational weeks in the late second-trimester	26.4±0.9	26.2±1.3	0.251
Urine ketones	3(0)	0	0.001

HG: hyperemesis gravidarum
p<0.05 is accepted as statistically significant

TABLE 2. Blood cell count data in the first trimester and at 24-28 weeks of gestation

Variables		HEG	Control	p
WBC (×10³/μl)	1st trimester	9.25 (2.90)	8.25 (2.35)	0.001
	late second-trimester	11.31 (2.31)	10.03 (3.67)	0.001
Hb (g/dl)	1st trimester	12.9 (1.23)	12.9 (1.25)	0.68
	late second-trimester	11.6 (1.5)	11.4 (1.4)	0.125
Hct (%)	1st trimester	37.8 (3.78)	37.5 (3.6)	0.356
	late second-trimester	33.7 (4.13)	33.6 (3.10)	0.242
NLR	1st trimester	4.54 (2.86)	3.66 (1.25)	0.021
	late second-trimester	4.89 (1.58)	4.05 (1.45)	0.010
PLR	1st trimester	155.79 (69.33)	128.75 (50.09)	0.001
	late second-trimester	135.28 (61.41)	119.10 (55.66)	0.032
RDW (%)	1st trimester	14.7 (27.5)	13.4 (1.8)	0.001
	late second-trimester	14.8 (2.7)	13.95 (2.10)	0.035
Plt (×10³/μl)	1st trimester	248 (76.25)	236 (68)	0.392
	late second-trimester	250 (72.25)	226 (86.25)	0.043

WBC: white blood cell count; Hb: hemoglobin; Hct: hematocrit; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; RDW: red blood cell distribution width; Plt: platelet
p<0.05 was accepted as statistically significant

RESULTS

A total of 355 pregnant women were included in the study. Table 1 shows the demographic characteristics of the patients and urine ketone values of the groups. Maternal age, gravidity, parity, and gestational weeks were similar in the two groups. The mean age of the women (27.42±5.03 years for the HG group, 26.54±6.9 years

TABLE 3. Two way repeated analysis of variance test results for each clinical parameter

	Effect	F	SD	p
WBC (×10³/μl)	group	3.68	1	0.041
	time	15.978	1	0.001
	group×time	23.120	1	0.001
Hb (g/dl)	group	2.319	1	0.133
	time	173.314	1	0.001
	group×time	1.031	1	0.314
Hct (%)	group	2.67	1	0.042
	time	150.475	1	0.712
	group×time	1.19	1	0.021
NLR	group	5.07	1	0.028
	time	4.079	1	0.034
	group×time	7.197	1	0.01
PLR	group	13.782	1	0.001
	time	9.346	1	0.003
	group×time	6.396	1	0.014
RDW (%)	group	19.401	1	0.001
	time	13.917	1	0.001
	group×time	10.898	1	0.001
Plt (×10³/μl)	group	8.596	1	0.005
	time	25.807	1	0.001
	group×time	1.000	1	0.321

WBC: white blood cell count; Hb: hemoglobin; Hct: hematocrit; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; RDW: red blood cell distribution width; Plt: platelet p<0.05 was accepted as statistically significant. The group effect shows whether the variable differs significantly between groups. The time effect shows that whether the variable significantly differs between two different time points. The group×time effect shows if an alteration of the variable is significant between two different groups at two different time points.

for the control group p=0.173), gestational age in the first trimester (9.2 (3.9) weeks for the HG group, 9.05 (3.4) weeks for the control group p=0.163) and in the late second trimester (26.4±0.9 weeks for the HG group, 26.2±1.3 weeks for the control group p=0.251) were similar in the two groups. Table 2 shows the complete blood cell count parameters of the study and control groups. The first and late second trimester WBC values were found higher in the HG group compared with the control group (first trimester WBC: 9.25 (2.90)×10³/μl vs. 8.25 (2.35)×10³/μl, p=0.001), (late second trimester WBC: 11.31 (2.31)×10³/μl vs. 10.03 (3.67)×10³/μl, p=0.001) (Table 2). The first and late second trimester NLR values were also higher in the HG group (first trimester NLR: 4.54 (2.86) vs. 3.66 (1.25), p=0.021), (late second trimester NLR: 4.89 (1.58) vs. 4.05 (1.45), p=0.01) (Table 2). There were no statistically significant differences of hemoglobin and hematocrit values between the two groups (Table 2). First trimester PLR values in the HG group (155.79 (69.33)) were higher than those in the control group (128.75 (50.09)) (p=0.001). In addition, late second trimester PLR values were also higher in the HG group (135.28 (61.41) vs. 119.10 (55.66), p=0.032). RDW values for the first and late second trimesters were also higher in the HG group compared to the control group (first trimester RDW: 14.7 (27.5)% vs. 13.4 (1.8)%, p= 0.001, late second trimester RDW values: 14.8 (2.7)% vs. 13.95 (2.10)%, p=0.035) (Table 2). In the present study, group effect, time effect (independent from group effect), and group×time interaction effects were statistically significant for WBC (p=0.041, p=0.01, and p=0.01, respectively), NLR (p=0.028, p=0.034, and p=0.01 respectively), PLR (p=0.001, p=0.003, and p=0.014, respectively), and RDW values (p=0.001 for all three effects) (Table 3). In addition, the group effect and time effect (independent from the group effect) were statistically significant for platelet values in the study (p=0.005 and p=0.001, respectively) (Table 3).

DISCUSSION

In the current study, WBC, NLR, PLR, and RDW values in the first and late second trimesters were found significantly increased in the HG group compared to the healthy pregnant women control group. The findings in the current study, that inflammatory markers in the late second trimester were higher than those in the first trimester, can be supportive of the premise that pregnant women with HG may have continuous systemic inflammation continues beyond the first trimester of pregnancy. PLR values were lower in both the HG and control groups in the late second trimester compared to the first trimester because mild thrombocytopenia occurs as a consequence of physiological hematological changes in the late second trimester. Despite this, PLR values were still detected higher in the HG group. Similarly, lower hemoglobin levels were observed in the late second trimester compared with the first trimester due to the disproportionate increase in the plasma and red blood cell volume, causing hemodilution in pregnancy.

Hyperemesis gravidarum is a condition of intractable nausea and uncontrollable vomiting with little or no relief throughout the day in pregnancy. Fluid, electrolyte and acid-base imbalance, and nutritional deficiency can arise in these patients due to long standing nausea and vomiting (3). This condition can also lead to malnutrition, severe dehydration, and weight loss that requires hospitalization. Although the etiology of the disease remains elusive, ample evidence suggests that inflammation plays a role in the pathogenesis of this condition (11, 20). In the study of Engin-Ustun et al. (11), women with HG were found to have significantly higher C-reactive protein (CRP) levels than those in the control group during the first trimester. Based on their results, Engin-Ustun et al. concluded that the presence of increased CRP levels in women with HG could contribute to the pathophysiological mechanism of HG, thus showing signs of the inflammatory process were present. Their finding was supported by study of Verit et al. (21). Another study has shown that interleukin-6 (IL-6), which is a cytokine produced primarily by activated monocyte/macrophages and T lymphocytes and involved in inflammation and immune responses, levels are increased in pregnant women with HG in the first trimester (20). It is assumed that increased IL-6 levels might be related to human chorionic gonadotropin secretion or placentation in pregnant women (22). Another explanation for this theory might be related to the high levels of serum inflammatory markers found in patients with HG as a result of either subclinical inflammatory response to the pregnancy or inflammatory responses engendered by pregnancy itself. Kaplan et al. (23) have compared the serum concentration of TNF-α, which is related to inflammation in the body, in patients with HG and in healthy pregnant women; and they found that HG patients have higher TNF-α levels than those in healthy controls, suggesting the immune system was involved in the etiology of HG. In agreement with our result, Kurt et al. (24) found that first trimester WBC, NLR, and CRP levels were higher in patients with HG compared to healthy pregnant wom-

en without HG. They also found that serum inflammatory markers were correlated with the severity of the disease. In addition to these findings, the effect of steroids, in terms of alleviating the symptoms related to HG (22, 25), can support the idea that inflammation plays a major role in the etiology of the disease (22). Even though steroids are proposed to exert their therapeutic effect through the chemoreceptor trigger zone in the brain stem, they probably taper off the inflammatory response in patients with HG, thus mitigating the symptoms of the illness.

Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and red blood cell distribution width are novel serum inflammatory markers with higher sensitivity than other serum inflammatory markers such as CRP and WBC (13, 26-28). These markers also increase in different obstetric conditions such as spontaneous preterm delivery or gestational diabetes mellitus (17, 24, 29, 30). Studies investigating the relationship between inflammation and HG are primarily focused on the inflammatory markers in the first trimester because HG predominantly occurs in this period. However, it is unclear whether the high inflammatory markers in patients with HG cause the disease or they are produced as a result of HG.

In this study, as distinguished from others, we evaluated the serum inflammatory markers in the late second trimester when symptoms of HG completely resolved, and we found that inflammatory markers were still high in the HG group during this period. This finding may point to a continuous systemic subclinical inflammation in patients with HG. However, conclusions drawn from our data cannot confidently be supported since the changes in serum inflammatory markers during the third trimester and the postpartum periods could not be evaluated due to extensive data loss. In addition, the inclusion of patients with nausea and vomiting that persist during all three trimesters to the study might help support our hypothesis. Unfortunately, we had to exclude these women from the study population due to the scarce number of these patients (only seven women). Therefore, we only assume that subclinical inflammation exists in pregnant women even after complete recovery from HG. However, our primary results require confirmation with future prospective experimental studies on the relationship between etiology of HG and serum inflammatory markers.

CONCLUSION

Pregnant women with HG develop subclinical systemic inflammation in the first trimester; and this condition exists in the late second trimester of pregnancy when all symptoms of HG disappear. This finding enables clinicians to implement appropriate intervention strategies regarding the treatment of HG.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Yıldırım Beyazıt University (22.07.2015, Decision No: 170)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Original Article

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Preclinical Medical Education in Turkey through the Students' Perspective and Knowledge of Research Activities

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BACKGROUND
Medical education is a long and difficult process. Nowadays, along with advances in communication technologies and the ease of access to information, new methodologies are applied too. However, the educational process shows that there are problems with training and guidance in Turkey.

MATERIAL and METHODS
An e-questionnaire was sent to randomly selected medical students enrolled on courses in Turkey in the 2014–2015 academic year. The students were questioned about their e-database using habits, and their views on research projects. The student responses were collected simultaneously in the database and the values in the database were assessed at every stage at instants in time.

RESULTS
The survey was conducted with the participation of 450 students. The majority of students stated that they attended lectures partial or full-time (90%). In total, 371 of the 450 students thought that the lectures were unsatisfactory. The number of students who needed additional resources were 273 (73.5%), and the proportion of those planning to take private lesson was very high (77.4%). Although education was given, the ratio of those using the e-database provided by the universities and The Scientific and Technological Research Council of Turkey (TUBITAK) was very low (17.4%). While only 15.4% students stated that they participated in article time activity, the proportion of students participating in research projects was higher at 30.9%.

CONCLUSION
Students stated that their received education is not enough and they needed to complement it with private courses, and also stated that the resources provided by the Government (universities and TUBITAK) were not sufficient. It is therefore clearly important to overcome the deficiencies and increase the guidance studies provided to students in Turkey.

Keywords: Medicine, education, e-database, Turkey

INTRODUCTION

Medical education is a long and difficult process. In order to make training more qualified, new methods are being used continuously. Studies are conducted to identify new teaching methods, interactive treatment modalities for increasing the success rate of students, and for identifying easy learning models (1). Today, integrated, interactive, and active teaching models are being used in different medical faculties (2). Advances in communication technology also offer new possibilities in the field of education. For this purpose, educational resources have been established for both educators and students. To reach universal standards, educators and students should use these facilities efficiently. The widespread use of these resources provides the availability of reliable information and an actuality of medical education. With access to the latest information and through the self-improvement of medicine students, the better education of qualified physicians can be achieved (3). Developments in the field of medicine are often rapid, and thus, sharing and following this knowledge will lead to the emergence of new ideas.

In Turkey, formal medical education takes 6 years. After this education, in order to be a specialist in a field of medicine, new doctors should pass a Medical Specialization Examination (MSE). In Turkey's Health Manpower Report, issued on March 2008, it was reported that a total of 50 private educational institutions also provide training for MSE (4). This suggests that the education in the medical schools is not enough for the students. The number of those in need of support for MSE is very high (5). This reveals that the sufficiency of the education given in the faculties of medicine should be questioned. As for the faculty teaching staff and student motivation, in this regard, it is aimed to develop these through training sessions and via conferences organized by various institutions.

This study was presented at the 9th National Medical Education Congress, 23 April 2016, İzmir, Turkey.

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In our study, the adequacy of the courses taken during the training of medical students, the study resources they prefer to use, the need for additional resources, information about the organizations, the provision of support for research, and knowing and using the e-database by students were all evaluated.

MATERIALS and METHODS

Study Design

Research was conducted via the participation of medical students belonging to 67 medical faculties out of 83 (63 government, 20 foundation), which is the total number of medical faculties in Turkey, enrolled on courses in the 2014–2015 academic year (6). These 67 faculties included 55 government and 12 foundation medical schools. Students included in the study were randomly selected among members of the Turkish Medical Students Association (TurkMSIC) and their faculty friends who were not members of TurkMSIC by social sites. They were informed about the study by a standard e-mail message and their consents were collected as e-data.

Data Collection Method

An e-survey was sent via e-mail to 1000 medical students. Totally, 450 of them answered the questionnaire. The survey was prepared in a format that began with 6 questions needing to be answered by each student, and then progressed after the sixth question with a scattered path according to the students' responses. While in some questions, the participant was requested to mark only one answer, in some of them multiple answers could be given. The students' responses were collected simultaneously in the database of the e-survey. The values in the database were evaluated at every stage instantly in the form of graphs and numerical data. The questionnaire was pilot tested on 50 medical students and all the questions worked without any problem.

In our survey, the students' satisfaction from their given medical education, their resource needs, what resources they used (with the usage rates of resources recoded in the e-databases and e-library), and to which additional resources they resorted to in the process of preparation for exams were questioned. They were also questioned about their knowledge about the research projects at medical faculties, the adequacy of equipment for a research project, and whether or not they were encouraged in undertaking these projects. The distribution of the data obtained was evaluated by considering whether the students were in a preclinical or clinical grade.

The survey was undertaken following the approval of the local ethics committee.

Data Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences, (SPSS Inc.; for Windows version 15.0; Chicago, IL, USA). The percentages of positive and negative answers were presented as valid percents.

RESULTS

Research was conducted by the participation of 450 medical students studying in the medical faculties in Turkey. The distribution of the classes and accreditation of the faculties are summarized in Table I.

TABLE I. The distribution of the classes of students who responded to the survey and accreditation of the faculties

The distribution of the class of the students (n: 450)	n (%)
Preclinical	415 (92.2)
Clinical	30 (6.6)
No response	5 (1.1)
Certificate of accreditation of the medical school	**n (%)**
Yes	252 (56)
No	194 (43)
No response	4 (3)

TABLE 2. The distribution of additional medical resources

Source selection	Always	Usually	Rarely	Never
Documents with Turkish translation	52	113	85	23
Documents in foreign languages	9	42	119	103
Notes taken during the lessons	164	90	15	4
Medical specialty exam books	10	55	107	101
Additional lecturer's notes	39	95	112	27

Used Documentary Resources and Education Satisfaction

The documentary resources used in theoretical and practical training were thought to be adequate by 72 (16%) of the medical students. However, 371 medical students (82.4%) thought that they were inadequate. In total, 273 (60%) students who indicated that their provided education was not enough were using additional resources (Table 2).

The majority of students (77.4%) were planning to take a private lesson for MSE because they did not find the given education sufficient for their examinations, while only 13.6% of the students did not plan on taking private lessons.

Use of the Internet

The question "For what purpose are you using the Internet?" was asked for the assessment of the use of technology and e-resources in medical education. Totally, 93% of the students stated that they were using the Internet for social media, while 91.9% of the students used it for communication and correspondence, 79.6% of them for research, 13.2% of them to benefit from the e-library, 26% to scan articles, and 36.1% to follow developments in medicine and in the world.

Use of an E-library

When we evaluated the results of the survey, only 30.6% of students stated that in their school, e-library training was given, while the majority (69.4%) stated that no e-library education was given in their school. While only 78 (17.4%) students responded positive to the question "Do you use an e-library?", most of them, 369 (82.6%), gave the answer "no." The reasons for not using an e-library were also asked about and the responses are given in Table 3.

Use of an E-database

In our survey those who were using an e-database were questioned about which resources they used and how they learned

TABLE 3. The distribution of the causes of student inability to use the e-library

Availability of the e-library	n (%)
Available	76 (16.9)
Unavailable	369 (82)
Not answered	5 (1.1)
Total	450 (100)
Reasons not to use the e-library*	**n (%)**
No information about usage	208 (71)
Lack of foreign language	57 (19.5)
Failure to provide access to documents	17 (5.8)
Lack of Internet access	4 (1.4)

*291 students gave answers

TABLE 4. Reasons of e-database non-users and the distribution of e-databases

Reasons of e-database non-users* (non-users n: 297, 66.4%)	n (%)
Never heard of it	101 (34.5)
Do not know how to use it	76 (25.9)
Lack of foreign language	79 (27)
Not interested	49 (16.7)
Want to get training	88 (30)
The distribution of e-databases* (users n: 150, 33.6%)	
Google Scholar	67 (43.5)
PubMED	140 (90.9)
Medscape	33 (21.4)
TUBITAK	38 (24.7)
UpToDate	19 (12.3)
Others	28 (18.2)

*Multiple choice questions
TUBITAK: The Scientific and Technological Research Council of Turkey

to use it, and those who did not use an e-database were questioned about their reasons. The obtained responses are summarized in Table 4.

Journal Club Activities

According to the responses given in the survey, 15.3% of the students stated that they attended a Journal club, while 84.7% of students stated that they did not attend.

Research Project

While the majority of the students (87.8%) wanted to take part in a research project, currently only 30.9% of them have participated in a project. Furthermore, while 26% of the students knew the organizations that support research projects, the rate of those who did not know was 74%.

When we finally asked "Do you think you would be competent at work with your current knowledge?", 77 (17.3%) of 444 medical students who answered this question though that they would be competent at work, while 367 (82.7%) thought not.

TABLE 5. The effect of being an accredited medical school on the study data

	Accredited medical school	Non-accredited medical school	p
E-library usage (n, %)			
Yes	75 (30)	60 (31)	0.82
No	177 (70)	132 (68)	
Not answered		2 (1)	
Journal club activities (n, %)			
Yes	33(13)	31(16)	0.91
No	43 (17)	35 (18)	
Have no idea	174 (69)	128 (66)	
Not answered	2 (1)		
Participation in a research activity			
Yes	75 (30)	59 (30)	0.91
No	179 (69)	135 (70)	
Not answered	1 (1)		

When all the answers were compared between the accredited and non-accredited medical schools, it was demonstrated that there was no significant difference between them (Table 5).

DISCUSSION

Our study demonstrates the thoughts of medical students about medical education in Turkey, MSE preparation schools and MSE books, the resources that the students use, knowledge about the e-library and e-database, and students' attention toward scientific projects and articles. Most of the students think that the education in the faculties is not sufficient for them and hence many are planning to take additional private lessons for MSE. These high numbers of displeasure of students toward their received education suggests that training skills should be revised and improved by the medical faculties in Turkey.

In Turkey, there are no studies evaluating medical education from the point of view of the students. With the detection of issues in medical education, studies on the solutions and the standardization of education are gaining in importance all over the world (3, 7). The Turkish Ministry of Health and professional organizations, such as the Turkish Doctors' Union, have published reports about this (4, 8, 9).

Most of the participants in our study stated that the education given in the medical faculties is not sufficient and they are using additional medical resources. Students' participation in lectures seemed quite high. Nevertheless, their thoughts about the inadequacy of those lectures are noteworthy. For this reason, they clearly question the adequacy of their knowledge and self-confidence in terms of professional skills.

Consequently, when we look at the overall student profile, 1st and 2nd grade students do not plan to take private lessons for MSE, but in the coming years, the vast majority of them were planning to take private lessons in order to be successful in the MSE.

Today, with the improvement of technology, it is very easy to access medical information. Internet use in the daily lives of the students was quite common. However, the Internet usage rates for professional development were not at the same level. Regarding this issue, universities and TUBITAK provide training on e-database usage. However, the usage of this e-database, as shown in our study, is still very low. In the study of Avcı et al. (10), it was demonstrated that 93.4% of students are social media users and 89.3% of them use social media for professional purposes. However, only the most popular social sites were asked about in this study: Facebook, Twitter, LinkedIn, medical blogs, and YouTube. The most used one was reported to be Facebook, even for professional purposes.

On the other hand, in our study, considering the students who do not use the e-database were also those who did not receive training, continuing their training is thus vital to increase the utilization rate. Not knowing English as a foreign language is also a barrier for using the e-database. Arranging additional courses for students will contribute to solving this problem.

Journal clubs and research activities are extremely useful for the improvement of the students' educational level. However, many students have expressed that there is no opportunities for this or they do not know about these activities in their faculties. At the same time, the number of students who are interested in research projects is quite high. However, the problems appear to be similar to the previous situation regarding participation. The usage of resources is extremely important for students in order to compete with other students and to become future scientists.

The accreditation of schools is very important for improving education. But it was demonstrated in our study that the ways of increasing knowledge about the worldwide medical science advances, such as through the e-database usage, reaching and reading research articles, or participating in a research are not different between the accredited and non-accredited schools. Obtaining this type of research training during medical education, especially in the accredited schools, will help improving education in the medical sciences.

CONCLUSION

In Turkey, according to students, the given education in medical schools is inadequate, and there is a trend to fill this gap with private lessons. Further, the availability of e-database sources is inadequate, and knowledge of the methodologies required by modern science is not widespread.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Muğla Sıtkı Koçman University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - A.Ö., S.B., C.K.; Design - C.K., S.B., P.Ç.; Supervision - C.K., S.B.; Data Collection and/or Processing - A.Ö., S.H., S.B., C.K.; Analysis and/or Interpretation - A.Ö., S.H., S.B., C.K.; Literature Search - A.Ö., S.B., C.K., S.H., P.Ç.; Writing - A.Ö., S.B., C.K., S.H., P.Ç.; Critical Reviews - S.B., C.K.

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Original Article

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Prevalence of an Azygos Lobe using Thoracic Computed Tomography

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BACKGROUND
An azygos lobe of the lung is a rare congenital venous malformation. It is usually detected using a chest X-ray, but computed tomography can also be used in selected cases for advanced examination and differential diagnosis. An azygos lobe is observed in high-resolution computed tomography images by 1.2%. We explored the prevalence of an azygos lobe using computed tomography at our hospital.

MATERIAL and METHODS
Computed tomography withdrawn by any reason was retrospectively evaluated using a picture archiving and communication system between September 2012 and November 2013 at Dörtyol State Hospital.

RESULTS
By examining thoracic computed tomography, the incidence of azygos lobe was found to be 1.54%. The incidence in woman and man was 1.39% and 1.64% respectively.

CONCLUSION
The frequency of an azygos lobe detected on performing computed tomography imaging was higher than that reported in the literature.

Keywords: Azygous lobe, thoracic computed tomography, prevalence

INTRODUCTION
An azygous lobe is a rare congenital anomaly located in the upper lobe of the right lung. Its incidence worldwide ranges between 0.2% and 1.2%. It develops in utero with the azygous vein passing anterior to the lung, resulting in the right apical lobe or posterior segment remaining behind the vein (1). This study aimed to quantify the frequency of an azygous lobe detected using thoracic computed tomography (CT).

MATERIALS and METHODS
We retrospectively analyzed 2.775 thoracic CT images at Dörtyol State Hospital between September 2012 and November 2013; images were accessed using a picture archive and communication system database. All CT images were acquired using a General Electric HiSpeed Dual Scanner (General Electric, Rosslyn, USA) during inspirium and while patients were in the supine position; the imaged area spanned from the apex to the diaphragm. Images were acquired in a single breath hold with 1-mm-thick slices and at 10-mm intervals W: 1500, L: -650. Written consent was obtained from all the patients. This study was exempt from ethics committee approval by Dörtyol State Hospital.

The IBM Statistical Package for Social Sciences version 23 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics for continuous variables are presented as digital and for categorical variable are presented as percentages.

RESULTS
In In total, 2.775 thoracic CT images, which were acquired during the specific period, were assessed. Of all thoracic CT images, 39% (n=1077) were of female patients, whereas 61% (n=1698) were of male patients. Using thoracic CT, the prevalence of an azygous lobe was determined to be 1.54% (n=43). The prevalence of an azygous lobe was 1.39% (n=15) in females and 1.64% (n=28) in males (Figure 1–5).

DISCUSSION
An azygous lobe is a rare anatomical variant that can manifest as significant morphological changes (2). It is generally seen in males. There is also a predilection for family inheritance (3, 4). The recognition of an azygous lobe is import-

This study was presented at the 17th Annual Congress of Turkish Thoracic Society, 2-6 April 2014, Antalya, Turkey.

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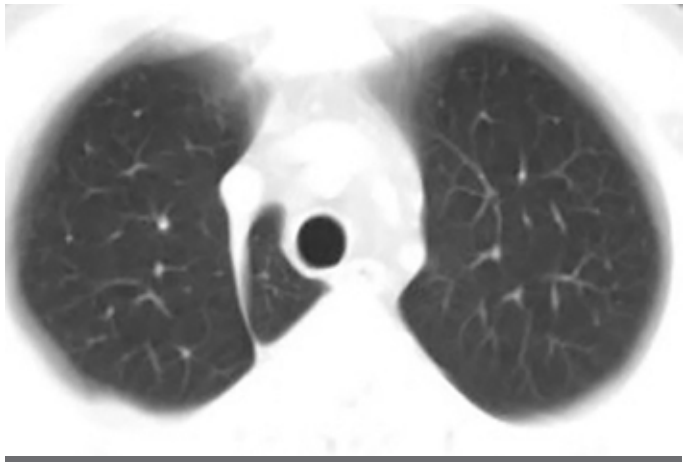

FIGURE I. Computed tomography axial image in different variations

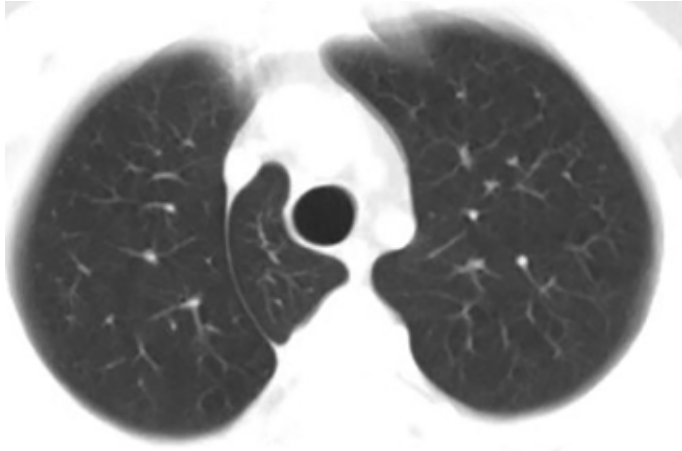

FIGURE 2. Computed tomography axial image in different variations

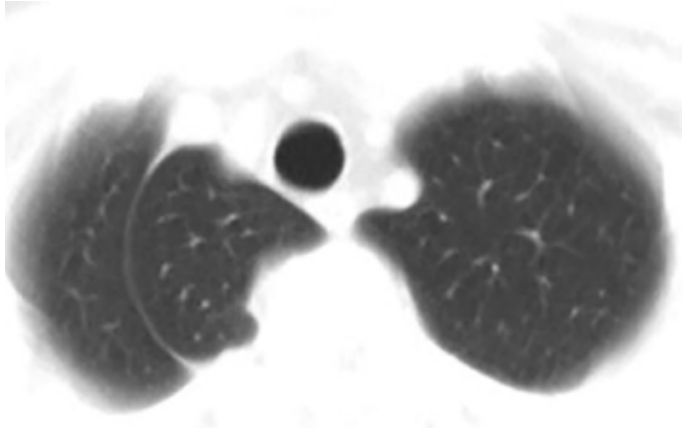

FIGURE 3. Computed tomography axial image in different variations

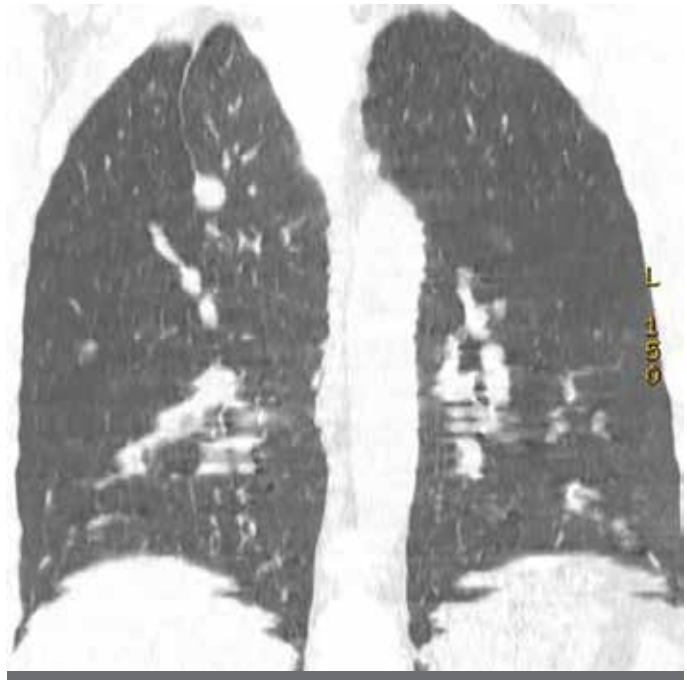

FIGURE 4. Computed tomography coronal image

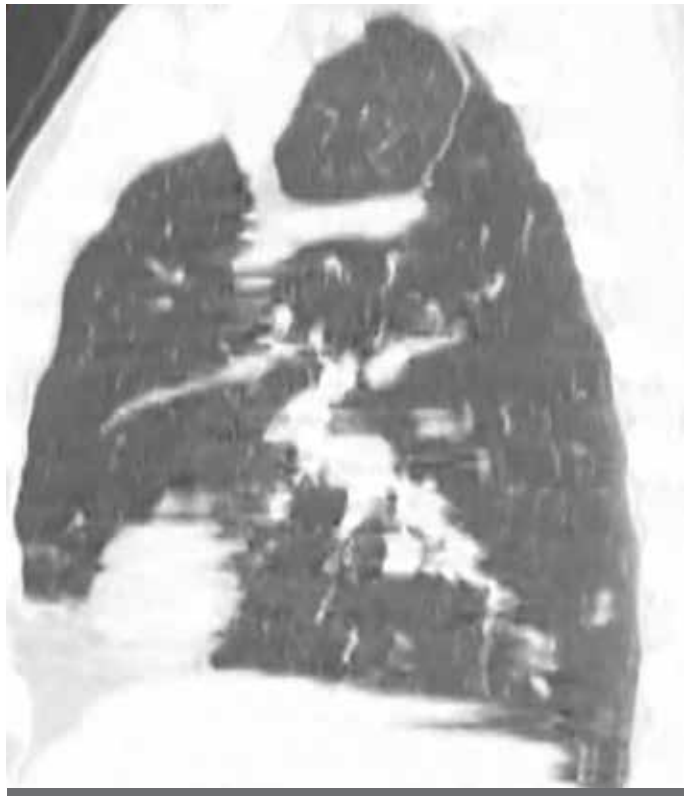

FIGURE 5. Computed tomography sagittal image

ant with regard to radiological reporting of imaging findings, assessing the course of pulmonary lesions and extent of pulmonary lesions, and the technical planning before performing thoracic surgery. An azygous lobe is usually incidentally picked up on imaging studies meant to investigate an unrelated pathology. The presence of an azygous lobe alone does not confer pathological significance; simultaneously occurring pathologies should be carefully considered. Despite the rare prevalence of an azygous lobe, there may be an association with pathologies such as fissures, tumors (small-cell lung cancers), extra-pulmonary sequestration, pneumothoraces, bullous changes, vascular anomalies, and situs inversus totalis. We did not detect a simultaneous pathology associated with the presence of an azygous lobe (5-7).

Despite many published reports regarding an azygous lobe, a limited number of studies have examined its prevalence, which is reported to be 1% in cadaveric specimens, 0.4% on plain chest X-rays, and 1.2% on high-resolution CT images (8-10). A PubMed search on the prevalence of an azygous lobe detected using thoracic CT images yielded a limited number of studies (10, 11). Thoracic CT images examined in our study yielded a case prevalence higher than that previously reported. In contrast to previous reports, we included and identified sex data. The prevalence of an azygous lobe in females was 1.39% (n=15) and in males was 1.64% (n=28)

The single limiting factor of this study was that it was conducted at a single center.

CONCLUSION

Our findings indicate that the prevalence of an azygous lobe was higher (1.54%) than that in other studies published in the literature.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - L.Ö., B.Ö., T.D.; Design - L.Ö., B.Ö., T.D.; Supervision - L.Ö., B.Ö., T.D.; Resource - L.Ö., B.Ö.; Materials - L.Ö., B.Ö.; Data Collection and/or Processing - L.Ö.; Analysis and /or Interpretation - L.Ö.; Literature Search - L.Ö.; Writing - L.Ö.; Critical Reviews - L.Ö., B.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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Effects of the Beginning of the Academic Year on Hospital Mortality: Is the July Phenomenon Real?

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BACKGROUND
It is suggested that in teaching hospitals, mortality rates are higher in the beginning of the academic year (July phenomenon) than in other months of the year. Differences in mortality rates have been reported according to working hours, weekdays, weekends, and off months. The aim of this study was to search for differences in mortality rates in intensive care units or clinics between working hours and night shift hours, weekends and weekdays, and off months and the months when residents start work.

MATERIAL and METHODS
From a total of 65.535 patients hospitalized in clinics and intensive care units of (blinded for peer review) between April 2009 and May 2015, data from 2.210 patients who died due to any cause were retrospectively evaluated. Patients' exitus frequencies were investigated to find a difference according to working hours/night shift hours, weekends and weekdays, and off months and the beginning of the academic year.

RESULTS
The rate of mortality in months when residents began to work was 47.3% and that in other months was 52.7% (p=0.98). The risk of mortality in months when residents began to work did not show significant difference compared with other months (Odds Ratio (OR): 1.001, 95% CI: 0.919–1.089; p=0.987). The mortality rate was lower in months when residents begin to work than in other months in the departments of surgical sciences (39.8% vs 60.2%, p=0.03), while the rates were similar in the departments of internal sciences and intensive care units.

CONCLUSION
The results of this study did not support literature data suggesting that the risk of mortality is higher in months when new residents begin to work in a training and research hospital.

Keywords: Academic medical centers, mortality, academic year

INTRODUCTION

It has been suggested that the rates of fatal medical errors, morbidity, and mortality increase in the beginning of the academic year when new residents begin their duties in training hospitals and that this may be due to the lack of clinical experience. This transition period has been defined as the "July phenomenon" in the United States of America and "killing August season" in the United Kingdom" (1-4). Conversely, numerous studies have reported that the rates of mortality and other complications in the beginning of the academic year are not different from those in other months and that the July phenomenon does not reflect reality (5-7).

This study aimed to investigate whether the risk of mortality shows an increase in months when new residents begin to work compared to other months.

MATERIAL and METHODS

From a total 65.535 patients hospitalized in clinics and intensive care units of the İstanbul Medeniyet University, Göztepe Training and Research Hospital between April 2009 and May 2015, data from 2.210 patients who died due to any cause were retrospectively evaluated. The study was approved by the ethical committee (Decision no: 2014/0092). Helsinki declaration principles were followed during the study.

Study Design

Patients' age and gender, date and hour of exitus, clinic/intensive care unit/emergency department in which exitus occurred, and death recordings were examined and recorded. The International Classification of Diseases was used in grouping the causes of hospital admission and death. The rates of mortality were compared between months when new residents began to work (December–February and September–November) and other months (March–June and

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October–November). The rate of mortality in the departments of internal sciences and surgical sciences and in intensive care units were further assessed.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software version 16 (SPSS Inc.; Windows, Chicago, USA). Variables were investigated using visual (histograms and probability plots) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk test) methods to determine whether they were normally distributed. Mortality frequencies in different academic periods [(December–February and September–November) and other months (March–June and October–November)] were assessed using the chi-square test and Fisher's exact test. Descriptive analyses were presented using mean and standard deviation as appropriate. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The number of patients who died due to any reason was 2,210 (1.208 males and 1.002 females, mean age: 54±30 years). The total number of hospitalizations was 31.498, and the number of patients who died was 1.259 (4%) in the departments of internal science, while this number was 241 out of 19.166 (1.3%) in the departments of surgical sciences and 710 out of 14.871 (4.8%) in intensive care units. The rate of mortality in the months when residents began to work was 47.3%, and the rate of mortality in the other months was 52.7% (p=0.98) (Figure 1). The risk of mortality in the months when residents began to work did not show a significant difference compared to the other months (OR: 1.001, 95% CI: 0.919–1.089; p=0.987). Mortality rate was lower in the months when residents began to work than in the other months in the departments of surgical sciences (39.8% vs 60.2%, p=0.03), while the rates were similar in the departments of internal sciences and intensive care units (Table 1).

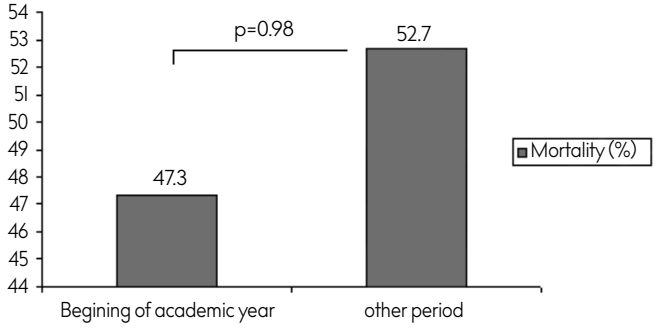

FIGURE 1. Rate of mortality in the months when residents began to work

TABLE 1. Comparison of the rate of mortality between months when residents began to work and other months

	Other months (n, %)		Months when residents began to work (n, %)		
	Number of hospitalizations	Number of exitus patients	Number of hospitalizations	Number of exitus patients	p
Overall mortality	34528 (52.7)	1164 (52.7)	31007 (47.3)	1046 (47.3)	0.98
Mortality in the departments of internal sciences	16607 (52.7)	655 (52.0)	14891 (47.3)	604 (48.0)	0.61
Mortality in the departments of surgical sciences	10207 (53.3)	145 (60.2)	8959 (46.7)	96 (39.8)	0.03
Mortality in intensive care units	7714 (51.9)	364 (51.3)	7157 (48.1)	346 (48.7)	0.74

Other months: March–June+October–November
Months when residents began to work: December–February+July–September

DISCUSSION

The results of this study showed that the rate of mortality in the months when new residents began to work was not significantly higher than in the other months.

It has been suggested that the rates of fatal medical errors, morbidity, and mortality increase in the beginning of the academic year when new residents begin their duties in training hospitals and that this may be due to the lack of clinical experience (1-4). In a study by Phillips et al. (3) all death certificates (n=62.338.584) in the United States of America between 1979 and 2006 were examined, and among 244.388 cases it was found that rate of fatal medical errors was greater by 10% in training hospitals than in those which are not training hospitals in July, which is the beginning of the academic year. In a retrospective observational study comparing the rates of mortality and complications between May and July in patients hospitalized in 98 training hospitals and 1.353 non-training hospitals in the United States of America due to acute myocardial infarction between 2000 and 2008, the rate of mortality was lower in May than in July, which is the beginning of the academic year, and that it was similar in training and non-training hospitals (8). It has been demonstrated in studies conducted in different clinics that the rate of adverse events in patients who have undergone anesthetic procedure, postoperative morbidity and mortality rates in patients hospitalized due to surgical reasons, and preventable or potentially preventable complications in patients hospitalized due to trauma were higher in the beginning of the academic year (4, 9, 10). There are studies showing that the beginning of the academic year is not effective on the rates of mortality and adverse events in training hospitals (11-13). It has been reported in a study evaluating life-saving treatments, diagnostic and therapeutic procedures, and in-hospital outcomes in patients hospitalized with a diagnosis of acute coronary syndrome and decompensated heart failure in July–September and November–January periods that there was no significant difference between patients hospitalized in both periods in terms of treatment characteristics and hospital mortality (14). Several retrospective cohort studies have evaluated whether poor clinical outcomes due to a lack of experience, particularly in intensive care units, surgical clinics, and transplantation and trauma centers, are seen more frequently in the beginning of the academic year and reported that mortality rates, hospitalization length, postoperative complications, and infection rates were similar to those observed in the other months of the year (15-18). In contrast, in our study, the rate of mortality in the months when new residents began to work (July–September and December–February) was similar to that in the other months. However, there are some differences affecting the comparison of our results with those from other

studies. The period when new residents begin to work is twice a year Turkey; the beginning of the academic year is in December–January or July–September. Therefore, it is not possible to compare the rate of mortality in a single month with that in other months as in other studies. In our study, the lower rate of mortality in the departments of surgical sciences in the months when new residents began to work than in the other months might be incidental as it might be related to the lower rate of hospitalization in the departments of surgical sciences.

Limitations of the Study

The most important limitations of this study were that the diagnoses of hospitalization and exitus, status of comorbidity, and characteristics of treatment could not be assessed in exitus patients.

CONCLUSION

A similar rate of mortality between the months when new residents began to work and the other months indicates that the beginning of the academic year is not effective on the rate of mortality.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Medeniyet University (Decision no: 2014/0092).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - O.A., M.U., A.O.; Design - M.U., A.O., O.A.; Supervision - A.O.; Resource - H.H.M.; Materials - O.A.; Data Collection and/or Processing - O.A., M.U.; Analysis and/or Interpretation - M.U., H.H.M.; Literature Search - O.T.C.; Writing - H.H.M., O.T.V.; Critical Reviews - O.T.C., A.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

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Autoamputated Fetal Adnexal Torsion Presenting as a Floating Abdominal Mass: Report of Two Cases

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An autoamputated fetal adnexal torsion is an extremely rare pathology in newborns that is frequently misdiagnosed as an ovarian cyst. Herein we present two cases of prenatally diagnosed fetal adnexal torsion that were successfully managed by laparoscopy. These cases suggest that this condition can be successfully managed by surgery, even in the neonatal period.

Keywords: Fetal adnexal torsion, ovarian cyst, neonatal period, laparoscopy

INTRODUCTION

Fetal adnexal torsion is a rare medical condition with various presentations. This condition is most commonly diagnosed during prenatal ultrasonography, and it requires a close follow-up due to serious complications such as intestinal obstruction and perforation (1). The treatment protocol is still debatable as there is no consensus between different authors due to the scarcity of cases. The most common approaches are early minimal invasive surgery, percutaneous cyst aspiration, or watchful waiting till spontaneous regression (2-7). All current approaches are debatable due to the lack of prospective randomized trials. Hereby we present two cases that were managed by early surgery in the light of documented literature on this issue.

CASE PRESENTATIONS

Case 1

A patient with a prenatally diagnosed intra-abdominal cystic mass was followed up at our department from birth. The cystic mass was 53×39 mm in size with debris inside. During the close radiologic follow-up, the mass changed its position from the left upper quadrant to the left lower quadrant. Its consistency and a cyst wall appearance with continuous displacement during ultrasonography led the radiologist to make a preliminary diagnosis of an enteric duplication cyst. The clinical course was uneventful until 15 days of age, when the patient developed continuous vomiting, restlessness, and abdominal distension. Emergency ultrasound showed an increase in mass size and a small amount of intra-abdominal fluid. Surgery was decided to be performed and the patient underwent diagnostic laparoscopy after providing informed consent. During exploration, a cystic mass attached with a fibrous band to the sigmoid colon was detected (Figure 1). Simultaneously, the right fallopian tube was rudimentary and the right ovary was absent. The left ovary was noted to be normal. The mass was laparoscopically excised (Figure 2). A pathologic examination revealed a complete necrotic cyst wall with no viable tissue inside. The postoperative course was uneventful, and the patient was discharged from the hospital on the next day following the surgery.

Case 2

A newborn with a prenatally diagnosed intra-abdominal cystic mass was referred to our hospital. The mass was 50×22 mm in size, with a solid component inside, and was located in the right upper quadrant. During an ultrasound investigation, the mass changed its original position and moved to the pelvis. The left ovary could not be visualized during the radiologic procedure. The patient was conservatively followed up for a month, and elective diagnostic laparoscopy was performed after obtaining informed consent. During exploration, the right ovary and fallopian tube were in place and were confirmed to have a normal morphology. The left ovary and fallopian tube were absent. The left fallopian tube was ending blind with no continuity and fimbrial ending. The cystic mass was discovered lateral to the descending colon and was presumably attached to the remnant of the ovarian ligament with a long thin fibrous band (Figure 3). The mass was excised, and its pathology showed total necrosis with no viable tissue inside the specimen (Figure 4). The postoperative course was unremarkable, and the patient was discharged from the hospital on the day following the surgery.

This study was presented as at the 31st National Paediatric Surgery Congress, 30 October-2 November 2013, Eskişehir, Turkey.

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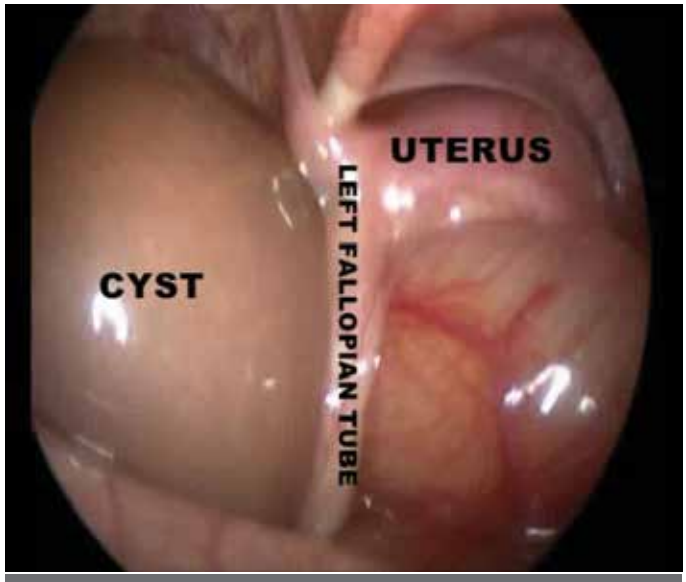

FIGURE I. Necrotic abdominal cyst (adnexal torsion) with its relation to the uterus and contralateral fallopian tube

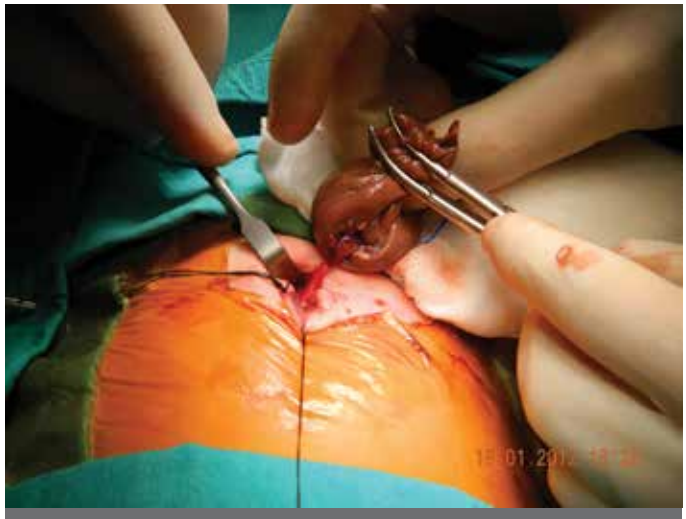

FIGURE 2. The removal of the cyst via an umbilical laparoscopy incision

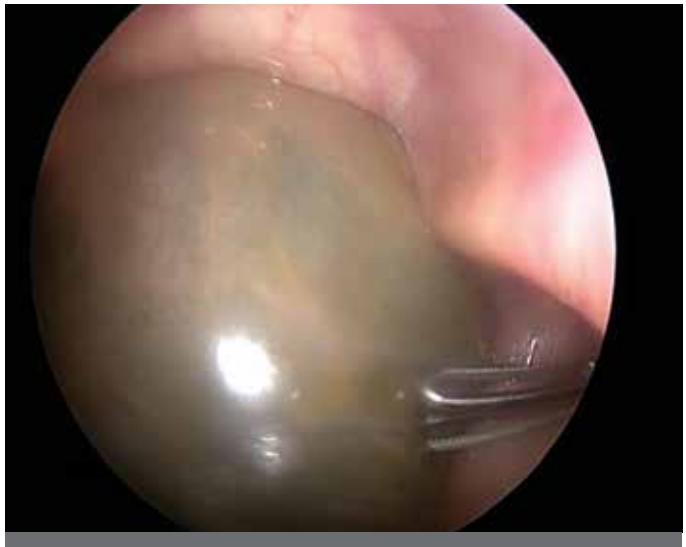

FIGURE 3. Necrotic abdominal cyst floating the abdomen

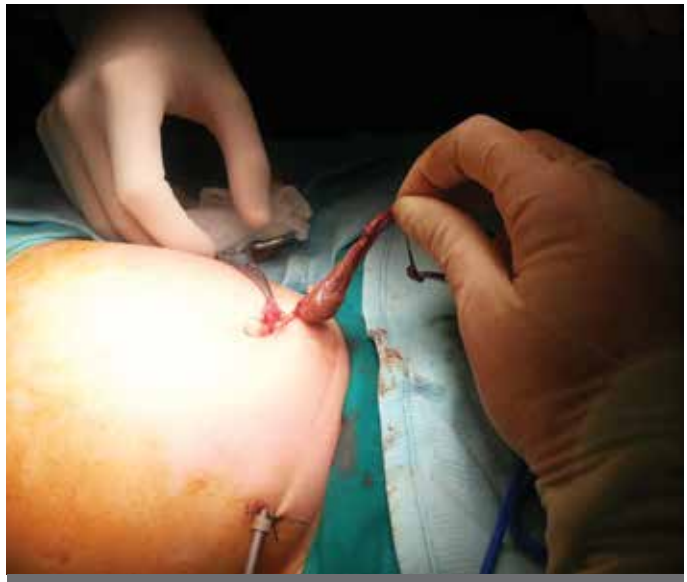

FIGURE 4. The removal of the cyst via an umbilical laparoscopy incision

FIGURE 5. The abdomen 6 months following surgery

DISCUSSION

Fetal adnexal autoamputation is one of the differential diagnoses among antenatal abdominal cysts in newborns. The etiology of this rare condition is most probably the intrauterine torsion of adnexal structures; however, the mechanism of torsion still remains unclear. Being first described in the 18th century during a postmortem study, surgeons paid close attention to its pathology; however, no clear consensus regarding the treatment and follow-up could be made due to scarcity of cases. Common approaches to the management of this condition are watchful waiting, percutaneous aspiration, and surgical removal. The percutaneous aspiration technique for infant ovarian cysts has been proposed by radiologists as a minimally invasive and safe technique. However, the remnant of the cyst wall left in the abdomen still poses a potential threat for intestinal adhesion and volvulus, and cyst recurrence is frequent (8, 9).

Watchful waiting seems to be a reliable approach, particularly in the newborn period. The literature suggests that simple

neonatal ovarian cysts tend to spontaneously regress (6, 9). Frequent ultrasonography follow-up and close monitoring for intestinal obstruction are mandatory in this approach. Complex cysts mostly require surgical intervention. Some authors propose that even autoamputated fetal adnexal torsion cases can be conservatively followed up until spontaneous regression (10).

The surgical approach has been proven to be a safe and reliable option, particularly after the introduction of minimal invasive surgery. Minimal invasive surgery diminishes concerns on postoperative scars and hospitalization duration (7). Laparoscopy in the newborn period with dedicated instruments diminishes the rate of complications related to the procedure itself. In our cases, we did not experience perioperative or postoperative complications. The patients were discharged uneventfully in a very short time.

Our cases support the minimally invasive surgical removal of auto-amputated fetal adnexal torsion in newborns. The procedure is performed in a short time with a short hospitalization duration. Simultaneously, the need for a prolonged follow-up is eliminated with this kind of approach. The cosmetic appearance after surgery is very satisfactory (Figure 5). We think that more cases are needed to form a guideline on the management of this condition.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Letter to Editor

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An Unusual Endoscopic Image of a Submucosal Esophageal Hematoma

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Dear Editor:

A 44-year-old man was referred to our department with hematemesis 2 days after swallowing an areca nut. Informed consent was obtained from the patient. The patient had no underlying disease. His laboratory test results revealed an elevated C-reactive protein level (13.85 mg/dL). Coagulation studies and liver and kidney function were normal. Endoscopy revealed an extensive, longitudinal, submucosal esophageal hematoma, extending from 20 cm past the incisors to the gastroesophageal junction. The lumen of the esophagus was moderately congested. No active bleeding or foreign body was observed (Figure 1). After 7 days of fasting and conservative treatment, an endoscopic follow-up revealed that the hematoma had completely resolved and that a shallow ulcer remained at the original lesion site (Figure 2).

An esophageal hematoma is a very rare phenomenon in clinical practice. Previous reports regarding the causes of esophageal hematomas have mainly referred to complications of endoscopy (1); other reported causes are hard food boluses, coagulopathy, trauma, drugs, or idiopathic causes (2, 3). Symptoms of esophageal hematomas are hematemesis, epigastric pain, heartburn, and odynophagia. The most important disorder to be differentiated is aortoesophageal fistula; however, these symptoms have also been reported in esophageal cancer, acute myocardial infarction, esophageal perforation, and aortic dissection.

The management of an esophageal intramural hematoma depends on the clinical situation. In most reports, patients respond well to conservative treatment. However, surgical intervention may be required during severe bleeding. We present these findings to increase awareness on imaging findings because a better understanding of risk factors may prevent misdiagnosis and inappropriate treatment.

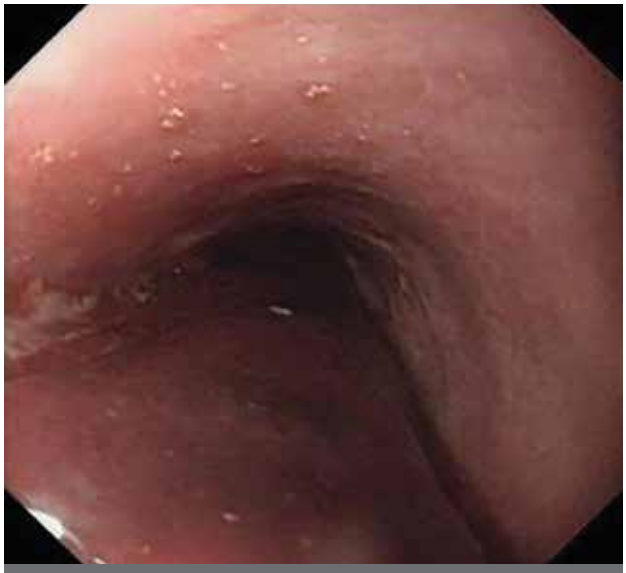

FIGURE 1. Endoscopy revealed an extensive, longitudinal, submucosal esophageal hematoma, extending from 20 cm past the incisors to the gastroesophageal junction

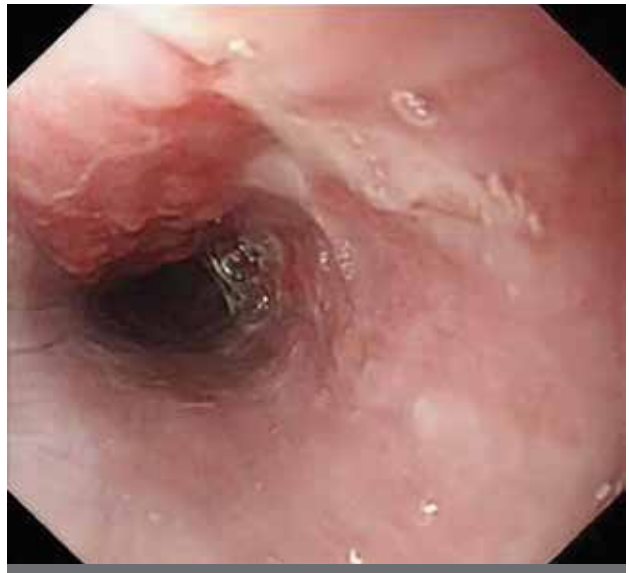

FIGURE 2. An endoscopic follow-up revealed that the hematoma had completely resolved and that a shallow ulcer remained at the original lesion site

This study was presented at the 15th Annual Conference of Guangxi Gastroenterology Society, 12-16 April 2015, Nanning, China.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Letter to the Editor

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Peliosis Hepatis in a Patient with Systemic Lupus Erythematosus

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Dear Editor,

Peliosis is a rare vascular condition of the parenchymatous organs characterized by the presence of blood-filled cystic spaces. Peliosis hepatis was first described in a 33 year-old woman with miliary tuberculosis (1). We presented a case of peliosis hepatis that has a rare association with systemic lupus erythematosus.

A 41-year-old woman was admitted to our center with complaints nausea, weakness, and anorexia for three weeks. She had a history of systemic lupus erythematosus (SLE) since 2008. The patient received a corticosteroid, and steroid-related diabetes mellitus (DM) occurred 4 years after the SLE diagnosis. In 2012, the patient was treated by a pulse steroid, rituximab, due to the hematologic involvement of SLE. Subsequently, she developed nephritis, cataracts, and central scotoma and avascular necrosis of the femoral head. Because of the abdominal swelling, abnormality in liver functions, and diffusely increased hepatic echogenicity, she underwent liver biopsy. Histologically blood-filled cysts were found in the parenchyma (Figure 1). The cavities were less than 1 mm in diameter, and they had no complete endothelial lining or fibrosis around cysts (Figure 2). The liver biopsy was interpreted as showing peliosis hepatis.

Gross examination revealed blood-filled cavities resembling "Swiss cheese". There are two microscopic types of peliosis hepatis. The first one is parenchymal peliosis, which is characterized by blood-filled, irregular spaces not lined by the endothelium or fibrous tissue. The second type, phlebectatica pattern, consists of blood-filled, regular, spherical cavities with an endothelial lining or fibrosis.

Peliosis hepatis is found in association with asphyxia, neoplasia, liver transplantation, renal transplantation, and drug therapy. A relationship between hematologic disorders and hepatic peliosis has been reported in the literature (2). Presenting case had a history of splenic artery embolization for idiopatic thrombocytopenic purpura ITP. A study demonstrated peliosis hepatis in six patients in an autopsy series for SLE (3). Langlet et al. (4) presented a patient with peliosis hepatis associated with SLE. SLE has a tendency to affect vessels. Interestingly, the association of SLE with peliosis hepatis is quite rare. It is arguable that presenting case this patient had more than one co-mor-

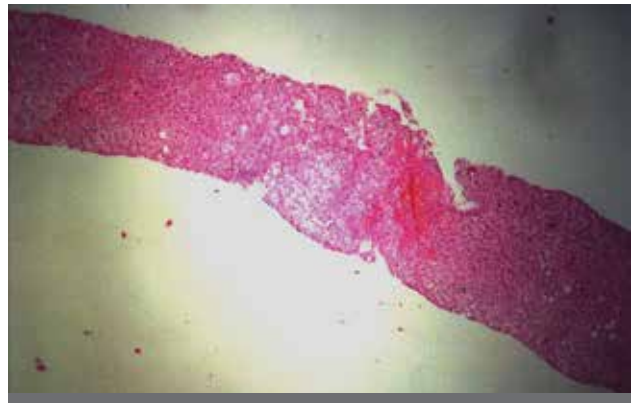

FIGURE 1. H& E, ×40, Blood-filled cystic spaces in the liver

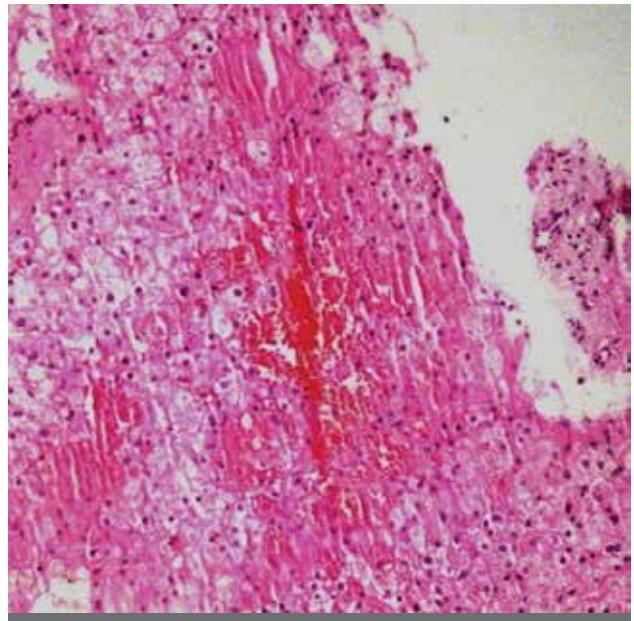

FIGURE 2. H& E, ×200, The cysts lack an endothelial lining or fibrosis

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bidity leading to peliosis hepatis. However, all these disorders were due to SLE or side effects of SLE therapy.

Usually, peliosis hepatis is incidentally detected. When it is symptomatic, severe clinical complications such as rupture and hemoperitoneum may occur. This rare entity must be kept in mind in the fatal course in symptomatic patients with abnormal liver function test results and abnormal radiologic features.

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Informed Consent: N/A

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Letter to the Editor

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Laparoscopy-assisted Transumbilical Removal of a Mesenteric Cyst in a Child

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Dear Editor,

Mesenteric cysts are rare intraabdominal benign tumors in children, the diagnosis of which is complicated by the absence of symptoms in majority of cases. Surgical removal is indicated to diminish the risk of bowel compression and intestinal obstruction (1-5). We present the case of a pediatric patient with a mesenteric cyst that was successfully managed with a laparoscopy-assisted technique.

A 3-year-old boy presented to the Emergency Department with complaints of recurrent abdominal pain and vomiting. Ultrasonographic examination revealed an abdominal cyst, measuring 8 cm, that displaced the ileal intestinal segments. The patient was preliminarily diagnosed with a mesenteric cyst/cystic lymphangioma, informed consent was taken and surgery was performed. A standard three-port laparoscopic technique that employed 5-mm trocars was performed. Laparoscopic exploration showed a cystic mass that originated from the ileal mesentery 70 cm proximal to the ileocecal valve. The mass compressed the neighboring intestinal segment from both sides. The cyst was aspirated for easier visualization and manipulation (Figure 1). After aspiration, the mass was removed via an umbilical incision, and standard intestinal resection with end-to-end anastomosis was manually performed outside the abdomen (Figure 2, 3). The postoperative course was uneventful, and the patient was discharged on the fourth day after the surgery. Pathological examination results were consistent with a mesenteric cyst.

This case indicates the importance of diagnostic laparoscopy and laparoscopy-assisted management even in complex cases that require intestinal resection in children.

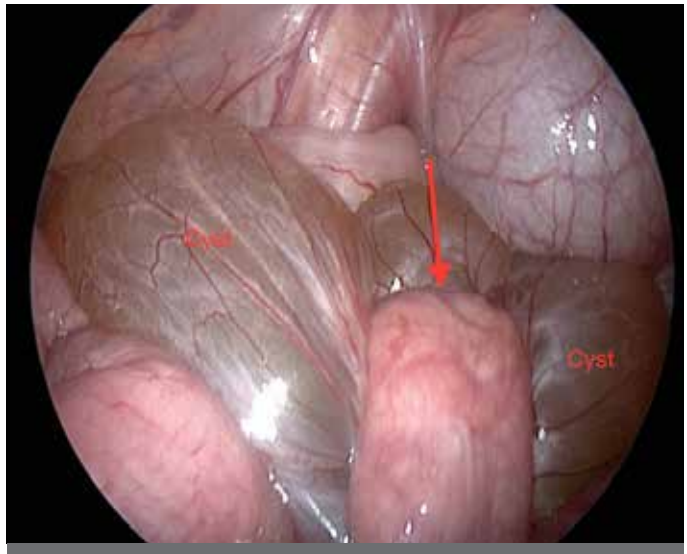

FIGURE 1. Laparoscopic view of the cyst that compressed the ileum from both sides (red arrow)

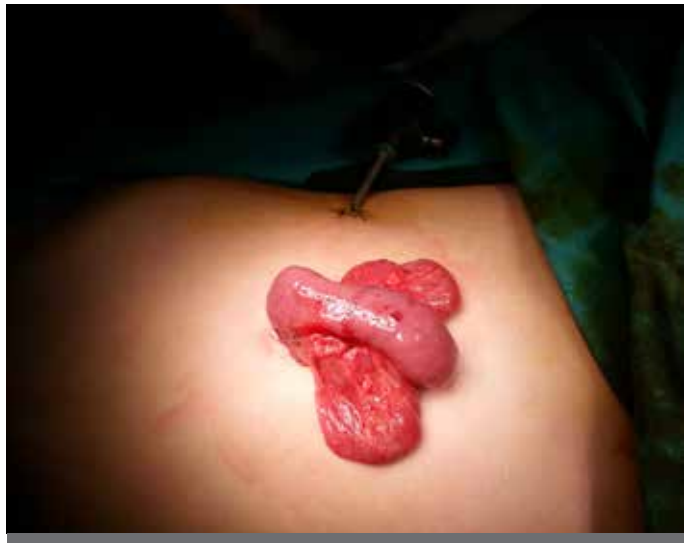

FIGURE 2. Aspirated cyst removed via an umbilical incision

This study was presented as a poster at the 32nd National Congress on Pediatric Surgery, 17-22 September 2014, Trabzon, Turkey.

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FIGURE 3. Excision of the cyst with complete adjacent bowel resection

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