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ORIGINAL RESEARCH

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The Utility of Serum Copeptin Levels for the Determination of Injury Severity and Prognosis in Adult Patients with Multiple Blunt Trauma

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Abstract

Objective: This study investigates the role of serum copeptin levels measured in the early post-traumatic period (first 24 hours) in adult patients with multiple blunt trauma (MBT) in determining trauma severity and the predicting prognosis.

Materials and Methods: This prospective cross-sectional study was enrolled 78 consecutive adult patients with MBT and 72 age- and sex-matched healthy controls with no acute traumatic injuries. The serum level of copeptin was assessed in all individuals were included in the study.

Results: No significant difference was observed between the patients with MBT and the control group in serum copeptin levels (3.13±6.10 vs. 3.90±6.82 and p=0.468). In addition, no statistically significant correlation was found between serum copeptin levels and age, revised trauma score (RTS), injury severity score (ISS), and Glasgow Coma scale values in patients with MBT. Additionally, no significant was observed difference between the hospitalized and discharged patients from the emergency department (ED) in terms of serum copeptin levels (1.72±3.05 vs. 1.95±3.50 and p=0.783).

Conclusion: In our study, trauma scores such as high RTS and low ISS values help determine the discharge from the ED in patients with multitrauma. However, we concluded that the serum copeptin level in these patients was not valuable in predicting trauma severity and prognosis in the early post-trauma period (in the first 24 hours).

Keywords: Multiple blunt trauma revised trauma score, injury severity score, prognosis, copeptin

Introduction

Biomarkers such as amyloid A, oxidative stress parameters, and atrial natriuretic peptides are an alternative to trauma scoring, and imaging methods are increasingly being used to evaluate the severity of injury in patients with multiple blunt trauma (MBT) [1]. Various scoring systems exist to evaluate trauma severity and prognosis in patients with MBT. Injury severity score (ISS) is the most predictive and reliable scoring for clinical development and prognosis, a scaled measurement indexed to anatomical injury: By scoring the damage done by trauma on each organ (with abbreviated injury score), the squares of the three highest-scoring values which is most severely injured body regions are added, and ISS is obtained [2], an ISS is greater than 15 represents major trauma. Bolorunduro et al. [3] categorized the ISS as follows. Bolorunduro et al. [3] categorized the ISS as follows. Less than 9 ISS is mild, 9-15 moderate, 16-24 severe, and above 24 profound. Copeptin, the precursor of arginine-vasopressin, is a glycopeptide consisting of 39 amino acids synthesized in the hypothalamus and is secreted from the neurohypophysis. The physiological function of circulating copeptin is still unclear [4,5]. Physiological stimuli such as pain or stress and pathological stimuli such as hypoglycemia, hypoxemia, stroke, infection, and shock cause copeptin release. Studies indicate that increased serum copeptin levels are associated with poor prognosis in many illnesses such as pneumonia, myocardial infarction, diabetes mellitus, heart failure, and stroke [6].

Therefore, we investigate the role of serum copeptin levels, a current marker of inflammation, measured in the early post-traumatic period (first 24 hours) in adult patients with MBT in determining trauma severity and the predicting prognosis.

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Materials and Methods

This prospective cross-sectional study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research and Hospital (trial registration no: 1472). This study was funded by the Health Sciences University Board of Scientific Research Projects (funding no: 2018/078). We study collected venous blood samples from consecutive patients with MBT who were admitted to our tertiary care university hospital emergency department (ED), within 24 h of trauma onset, between October 2018 and January 2019. Seventy-eight consecutive adult patients with MBT (16 females and 62 males, age range 17-92 years) due to various causes (vehicle accidents, vehicle-pedestrian accidents, falling from a height, or assault) as the primary injury, and 72 age- and sex-matched healthy controls with no acute traumatic injuries, were included in the study. Adults exposed to multitrauma were first hemodynamically stabilized and a standard advanced trauma life support (ATLS) protocol was applied to each patient as suggested in the current 2018 ATLS-10 guidelines [7].

After vital functions had been monitored, written informed consent was obtained directly from the patient or from their authorized representative. Healthy volunteers were informed about the study protocol, and written consent was obtained from all participants before their participation in the study. The inclusion criteria were adult patients (≥18 years of age) with MBT. The revised trauma score (RTS), Glasgow Coma scale (GCS), and ISS values were calculated for each patient. Patients were divided into two groups: Those with ISS <25 (group 1; mild to severe trauma) and ISS ≥25 (group II; profound trauma).

Blood samples were drawn from the antecubital vein of each subject immediately after presentation to the ED; samples were immediately placed on ice at 4°C without the use of medications or serum infusions and collected in vacuum gel tubes. Plasma was separated from the cells by centrifugation at 2515×g for 10 min using a centrifuge (Electro-mag M615E, Istanbul, Turkey) and immediately stored at -80°C until the analysis of serum copeptin levels. Serum level of copeptin was assessed in MBT patients and healthy controls. It was estimated that at least 78 participants and 72 controls would be required to detect significant differences among the patient groups with a power of 95% and an alpha error of 5%.

Statistical Analysis

The data collected in the study were analyzed using SPSS 15.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive statistics are expressed in numbers and percentages of categorical variables. Numerical variables are expressed as the mean, standard deviation, and minimum and maximum values. The numerical variables in the two independent groups were compared using the Student independent t-test (comparison of copeptin level) when the data conformed to normal distributions. When the data were not normally distributed, the Mann-Whitney U test was used to compare two independent groups (e.g., age and gender). The ratios in the groups were compared using the chi-square test. Pearson's correlation coefficient was used to evaluate any correlation between ISS or RTS values and data that were normally distributed (serum level of copeptin). The significance level was set at $p<0.05$.

Results

A total of 78 adult patients with MBT, 62 male (79.5%) and 16 female (20.5%), were conducted in the study. The control group included 72 healthy volunteers, 49 (77.8%) were male and 14 (22.2%) female. The mean age of the patients with MBT was 37.10±17.70 (age range; 17-92); the mean RTS value was 7.70±1.10, mean ISS 24.0±13.30, and mean GCS 13.8±3.1.

Table 1 shows the mechanisms of injury in patients with MBT in our study. There were falling from height in 28 patients, motor vehicle accidents in 17 patients, assault in 18 patients, motor vehicle-pedestrian accidents in 9 patients, and motorcycle accidents in 6 patients.

No significant difference was observed between the patients with MBT and the control group in terms of serum copeptin levels (3.13±6.10 vs. 3.90±6.82 and p=0.468). In addition, no statistically significant correlation was found between serum copeptin levels and age, RTS, ISS, and GCS values in patients with MBT (Table 2). Twenty-five patients (32%) were hospitalized, and 53 (68%) were discharged from the ED. Mean

Table 1. Causes of multiple blunt trauma in patients admitted to the emergency department

		n	%
Cause of multiple blunt trauma	Fall from a height	28	36
	Motor vehicle crash	17	22
	Assault	18	23
	Motor vehicle-pedestrian crash	9	12
	Motorcycle crash	6	7

Table 2. Correlation between serum copeptin level and age, RTS, ISS and GCS values

	Copeptin (ng/mL)	
	rho	p*
Age	-0.175	0.125
RTS	0.044	0.700
ISS	-0.065	0.571
GCS	0.127	0.267

*ISS, RTS, GCS, serum copeptin values and age were calculated by Pearson correlation test. RTS: Revised trauma score, ISS: Injury severity score, GCS: Glasgow Coma scale

ISS values were significantly elevated, whereas mean RTS values were significantly decreased in hospitalized patients compared to discharged patients (p=0.025 and p<0.001; Table 3). In addition, the mean age of the hospitalized patients was lower than discharged patients from the ED (30.70±13.00 vs. 38.70±18.10 and p=0.036; Table 3).

However, no significant difference was observed between the hospitalized and discharged patients from the ED in terms of serum copeptin levels (1.72±3.05 vs. 1.95±3.50 and p=0,783; Table 3). When patients were evaluated with ISS scores in terms of trauma severity; there was no statistically significant difference in age, gender, and serum levels of copeptin between patients with ISS <25 and ISS ≥25 (p=0.355, p=0.260, and p=0.595, respectively; Table 4).

Discussion

Molecular studies indicate that copeptin, as a biochemical parameter, plays an important role in the pathogenesis and progression of acute critical diseases [8]. Although many studies investigate serum copeptin levels in several non-traumatic diseases, there are limited clinical studies investigating the serum level of copeptin in acute traumatic situations and predicting trauma severity and prognosis. These studies have been performed in isolated head trauma patients [9]. In a study conducted by Westermann et al. [10], endogenous vasopressin and copeptin levels in patients with MBT were compared with the healthy group. However, no study investigated the role of copeptin levels in predicting trauma severity and prognosis in the early posttraumatic period within 24 hours. Therefore, our study is the first research to analyze the serum copeptin level in MBT patients and the role of copeptin levels in predicting trauma severity and prognosis in the first 24 hours.

İpekci et al. [11] included 82 cases with multiple trauma. They observed that the value of copeptin on admission to ED was significantly higher in multi-trauma cases than in the control group. The level of copeptin decreased significantly after 24 hours. In our study, similar to İpekci et al. [11] , there was no statistically significant difference between the patient with MBT and healthy individuals regarding mean serum copeptin levels. In addition, no significant correlation was observed between serum copeptin level and trauma scores, including RTS, ISS, and GCS values.

In a study that included 105 patients with moderate head trauma, Castello et al. [12] reported no significant correlation between the serum copeptin levels and the age of the patients. Similarly, we observed no significant correlation between copeptin level and age.

In a study that compared plasma copeptin levels of 87 trauma patients with healthy controls, Westermann et al. [10] found that copeptin levels were significantly higher in patients with MBT than the healthy controls. Another study by Dong et al. [9] investigated posttraumatic plasma copeptin levels in patients with head trauma and observed that copeptin increased in the first six hours after trauma and peaked within 2 hours. Unlikely, no statistically significant difference was found between the patient and control groups in terms of mean serum copeptin

Table 3. Comparison of age, gender, and serum copeptin levels between the hospitalized and discharged patient groups

	Hospitalized (n=25, 32%)	Discharge (n=53, 68%)	
Characteristic	**Mean ± SD**	**Mean ± SD**	**p***
Age	30.70±13.00	38.70±18.10	0.036
RTS	7.00±1.80	7.90±0.30	0.025
ISS	35.70±16.30	18.10±1.70	>0.001
Copeptin (ng/mL)	1.72±3.05	1.95±3.50	0.783

Data are expressed in numbers, percentages, and mean ± SD. *The Mann-Whitney U test was used to compare the age and gender distribution between groups, and Student's t-test was used to compare serum copeptin levels between groups. SD: Standard deviation, RTS: Revised trauma score, ISS: Injury severity score

Table 4. Comparison of age, gender, and serum copeptin levels between the ISS <25 and ISS ≥25 patient groups

		ISS <25 (n=61)	ISS ≥25 (n=17)	
Characteristic		**Mean ± SD**	**Mean ± SD**	**p***
Age		38.10±17.90	33.60±16.90	0.355
Gender	**Male**	47 (77%)	15 (88.2%)	0.260
	Female	14 (23%)	2 (11.8%)	
Copeptin (ng/mL)		3.53±6.46	3.31±6.62	0.595

Data are expressed in numbers, percentages, and mean ± SD. *The Mann-Whitney U test was used to compare the age and gender distribution between groups, and Student's t-test was used to compare serum copeptin levels between groups. SD: Standard deviation, ISS: Injury severity score

level in our study. In addition, there was no significant correlation between serum copeptin levels and trauma scores. Copeptin is released simultaneously from the neurohypophysis via osmotic or hemodynamic stimulus. There were few cases with traumatic brain injury and hemodynamically unstable in our study. More studies investigating the role of serum copeptin levels in patients with MBT are needed.

Conclusion

In conclusion, considering the findings obtained in our study, trauma scores such as high RTS and low ISS values are useful in determining the discharge from the ED in patients with multitrauma. However, we concluded that the serum copeptin level in these patients was not valuable in predicting trauma severity and prognosis in the early post-trauma period (in the first 24 h).

Ethics

Ethics Committee Approval: Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research and Hospital (trial registration no: 1472).

Informed Consent: Written informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.A., A.A., T.Ak., Concept: Ö.S., Design: T.A., Ö.S., Data Collection or Processing: T.A., A.A., T.Ak., Analysis or Interpretation: T.A., Ö.S., Literature Search: T.A., A.A., Writing: T.A., A.A., T.Ak., Ö.Ö.

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

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ORIGINAL RESEARCH

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The Effect of Serum Lactate Level and Shock Index on Morbidity and Mortality in Aortic Dissection and Aneurysm

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Abstract

Objective: Acute aortic dissections and aneurysms are vascular emergencies and have high mortality rates. Since early diagnosis is valuable in terms of mortality and prognosis, the effects of shock index (SI) and lactate levels on mortality and prognosis in patients with aortic dissection or aneurysm were investigated.

Materials and Methods: The study was conducted by retrospectively examining 71 patients older than 18 years, who were diagnosed with aortic dissection or aneurysm, who applied to the emergency department between January 01, 2015, and December 31, 2020. The patients were divided into two groups in terms of dissection and aneurysm. Three groups were defined for dissections and two groups for aneurysms. Age, gender, lactate level, SI, and mortality of the patients were evaluated.

Results: The mean age of the 71 patients included in the study was 62.08±13.80 years, 15 (21.1%) were female, and the age range was 32-94 years. Lactate levels of aortic dissection and abdominal aneurysm cases were 3.22±2.09 mmol/L and 1.90±1.51 mmol/L, respectively (p=0.004). The mean shock indices of patients with aortic dissection and aneurysms were 0.71±0.18 and 0.63±0.15, respectively (p=0.018). While 19 (54.2%) of 35 cases with aortic dissection survived, 16 (45.8%) died. While 30 (83.3%) of the aortic aneurysm cases survived, 6 (25%) died (p=0.008).

Conclusion: SI and serum lactate levels may be prognostic values in terms of morbidity and mortality in aortic dissection and/or aortic aneurysm.

Keywords: Emergency department, aortic dissection, aortic aneurysm, SI, serum lactate level

Introduction

Acute aortic dissections (AAD) are a dramatic life-threatening disease. It is defined as the separation of the media and intima layers of the aorta along the long axis of the vessel. It is one of the leading diseases in terms of mortality and morbidity. Aortic dissection, one of the most urgent cardiovascular diseases, requires rapid diagnosis and treatment. Appropriate diagnosis and treatment methods should be used to prevent this sudden-onset pathology from becoming fatal. AAD are estimated to occur with a frequency of 5-10/1,000,000 in the United States [1]. Unfortunately, there is no large-scale incidental study in our country. Mortality in the first two weeks is approximately 80-90% in patients with AAD due to failure to diagnose or delay in treatment. It has been reported that mortality increases by approximately 1-3% per hour in the first two days [2]. The incidence of the disease is higher in men than in women. Many predisposing factors and etiological causes can be shown as precursors for damage to the aorta and dissection. These etiological and predisposing factors are currently accepted under seven main headings. These; hypertension, medial degenerative disease, congenital anomalies, atherosclerosis, inflammatory diseases, trauma, and pregnancy [3]. According to DeBakey's et al. [2] definition of dissection, it is defined as acute in the first 14 days, subacute between 15 days and 60 days, and chronic if it lasts longer than 2 months.

Clinical suspicion is the most important step for the diagnosis of aortic dissection, which is one of the most life-threatening diseases. In reaching the diagnosis, anamnesis, physical

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examination and telecardiography are important steps. However, the specificity of telecardiography in the diagnosis of aortic dissection is low [4]. Clinically, typical symptoms of aortic dissection are sudden onset, tearing, severe, chest pain that starts from the back and neck and spreads to the jaw [5]. However, patients with aortic dissection do not always present with these classic symptoms. It has been reported that some patients did not describe any pain, and some patients with pain did not present with classical complaints. Although diagnosis is delayed in these patients who do not present with classic symptoms and have atypical complaints, there an increase in mortality rates [6].

Patients diagnosed with AAD and aneurysm have high morbidity and mortality rates. Therefore, it was determined the effect of shock index (SI) and serum lactate levels on mortality in patients with aortic dissection and aneurysms who applied to the emergency department.

Materials and Methods

Population and Laboratory Design

In this retrospective study, the data of 71 patients (mean age 62.08±13.79 years, mean range 32-94 years) diagnosed with aortic dissection and aneurysm in the emergency department between January 01, 2015, and December 31, 2020, were included. The patients were selected from those whose clinical findings, vital signs, serum lactate levels, and diagnostic data were recorded in the hospital data recording system. Patients under the age of 18 and patients with insufficient data were excluded from the study.

Age, gender, SI, serum lactate levels, hematological parameters, and urea and creatinine values were recorded from the patient files. Hemograms were measured using a Beckman Coulter Automated CBC Analyzer (Beckman Coulter, Inc., Fullerton, CA, USA). Biochemistry blood was analyzed with a Cobas 6000 (C6000-Core, Cobas c-501 series, Hitachi, Roche, USA). Venous blood gas samples were taken for lactate level. Patients' lactate levels were obtained from venous blood gas analyses using the Cobas® b221 blood gas system (Roche, Basel, Switzerland).

The SI was calculated based on the vital signs of the patient at the time of admission to the emergency room. The formula "SI: Heart rate (HR) (HR/minute)/systolic blood pressure (SBP) (mmHg)" was used.

Dissection types were grouped according to the DeBakey (types 1, 2, and 3) classification. According to the DeBakey classification, type 1 dissection is seen in the entire aorta, type 2 dissection is seen only in the ascending aorta, and type 3 dissection is seen in the descending aorta [7]. The aneurysm patients were determined as ascending and descending. Groups were determined according to mortality or not.

The study was conducted in accordance with the Helsinki Declaration of Human Research after the approval of the Health Sciences University, Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee (subject number: KAEK/2022.02.41, decision no: 41, date: 23.02.2022). After all, patients were informed, their consent was obtained for inclusion in the study.

Statistical Analysis

The data obtained from the study were analyzed with the SPSS 20 (SPSS Inc., Chicago, IL, USA) package program. The Kolmogorov-Smirnov test was used while investigating the normal distributions of the variables. Descriptive statistics and continuous variables were presented as mean ± standard deviation or median (minimum-maximum) and nominal variables were presented as many cases and percentage (%). While examining the differences between the groups, Mann-Whitney U and Kruskal-Wallis H tests were used because the variables did not come from a normal distribution. Chi-square analysis was performed when examining the relationships between groups of nominal variables. Spearman's rho analysis was used for correlation with variables. Receiver operating characteristic (ROC) curve was used for sensitivity and specificity analysis of dissection, aneurysm, and mortality. When interpreting the results, values below the significance level of 0.05 were considered statistically significant.

Results

The mean age of all patients was 62.08±13.79 years, and the mean range was 32-94 years. The mean age of patients with aortic dissection or aortic aneurysm was 56.74±14.01 years and 67.27±11.56 years, respectively (p=0.001). The mean serum lactate levels of the cases were 3.22±2.09 mmol/L and 1.90±1.51 mmol/L, respectively (p=0.004). The mean shock indices of the cases were 0.71±0.18 and 0.63±0.15, respectively (p=0.018). The mean hematocrit values of the patients were found to be 35.58±6.51% and 32.46±6.07%, respectively (p=0.046). Seventy one patients were included in the study. Fifty six of these cases (78.8%) were male. The relationship between gender and group was not significant (p=0.132, Table 1).

In the subtypes of aortic dissection in the study, the mean ages for type 1, type 2, and type 3 dissections were 59.14±13.97 years, 63.42±10.75 years, and 42.85±6.96 years, (p=0.001), serum lactate levels were 3.49±2.05 mmol/L, 2.65±1.80 mmol/L, and 2.95±2.61 mmol/L, (p=0.025) and SIs of the cases were 0.75±0.19, 0.64±0.19, and 0.66±0.13, respectively (p=0.032). Of 21 patients with type 1 dissection, 9 (42.8%) survived, while 12 (57.8%) died. While 5 (71.4%) of 7 cases with type 2 dissection were alive, 2 (28.6%) died. While 5 (71.4%) of 7 patients with type 3 dissection were alive, 2 (28.6%) died (p=0.020, Table 2).

Table 1. Evaluation of age, gender, shock index and laboratory variables with aneurysm and dissection groups

		All patient mean ± SD	Dissection mean ± SD	Aneurysm mean ± SD	p value*
Age (year)		62.08±13.79	56.74±14.01	67.27±11.56	**0.001**
Lactate (mmol/L)		2.55±1.93	3.22±2.09	1.90±1.51	**0.004**
Shock index		0.67±0.17	0.71±0.18	0.63±0.15	**0.018**
Urea (mg/dL)		50.98±34.90	48.27±24.52	53.61±42.84	0.845
Creatinine (mg/dL)		1.34±1.07	1.24±0.63	1.43±1.37	0.516
Sodium (mmol/L)		140.25±6.60	140.44±7.12	140.07±6.11	0.945
Potassium (mmol/L)		4.16±0.65	4.09±0.61	4.23±0.69	0.486
WBC (×10³/mcL)		12.95±6.20	14.25±7.37	11.69±4.56	0.110
Hemoglobin (g/dL)		11.16±2.24	11.66±2.27	10.67±2.12	0.086
Hematocrit (%)		34.00±6.44	35.58±6.51	32.46±6.07	**0.046**
MCV (fL)		87.29±5.70	87.44±5.83	87.15±5.64	0.730
MCHC (g/dL)		32.23±1.68	32.06±1.46	32.39±1.87	0.309
PLT (×10³/mcL)		207.59±108.82	220.64±130.9	194.91±81.82	0.585
Gender		**n (%)**	**n (%)**	**n (%)**	**p value****
	Male	56 (78.8)	25 (71.4)	31 (86.1)	0.132
	Female	15 (21.2)	10 (28.6)	5 (13.9)	
	Total	71 (100)	35 (100)	36 (100)	

*Mann-Whitney U test, **Chi-square analysis, WBC: White blood cell, MCV: Mean cell volume, MCHC: Mean corpuscular hemoglobin concentration, PLT: Platelet, SD: Standard deviation

Table 2. Relationship of variables with aortic dissection types

		Type 1 dissection mean ± SD	Type 2 dissection mean ± SD	Type 3 dissection mean ±SD	p value*
Age (year)		59.14±13.97	63.42±10.75	42.85±6.96	0.001
Lactate (mmol/L)		3.49±2.05	2.65±1.80	2.95±2.61	0.025
Shock index		0.75±0.19	0.64±0.19	0.66±0.13	0.032
Urea (mg/dL)		52.83±25.12	47.61±26.79	35.25±17.78	0.364
Creatinine (mg/dL)		1.37±0.74	1.01±0.36	1.10±0.43	0.568
Sodium (mmol/L)		139.70±6.72	141.85±9.75	141.28±6.07	0.807
Potassium (mmol/L)		4.14±0.60	4.24±0.50	3.79±0.72	0.501
WBC (×10³/mcL)		13.61±5.74	10.68±3.83	19.72±11.48	0.073
Hemoglobin (g/dL)		11.55±2.02	12.02±2.55	11.62±3.01	0.367
Hematocrit (%)		35.36±5.48	36.91±7.08	34.91±9.34	0.245
MCV (fL)		87.19±6.34	88.40±4.94	87.22±5.73	0.956
MCHC (g/dL)		31.90±1.52	31.54±1.28	33.07±1.10	0.151
PLT (×10³/mcL)		206.14±125.74	232.00±123.53	252.78±164.64	0.772
		n (%)	**n (%)**	**n (%)**	**p value**
Mortality	**No**	9 (42.8)	5 (71.4)	5 (71.4)	**0.020**
	Yes	12 (57.8)	2 (28.6)	2 (28.6)	
	Total	21 (100)	7 (100)	7 (100)	

*Kruskal-Wallis H test, **Chi-square analysis, WBC: White blood cell, MCV: Mean cell volume, MCHC: Mean corpuscular hemoglobin concentration, PLT: Platelet

The mean age in ascending and descending aortic aneurysms was 50.33±20.84 years and 68.81±9.47 years, respectively (p=0.001). Serum lactate levels were 1.33±0.32 mmol/L and 1.95±1.57 mmol/L (p=0.013). Mean corpuscular volume (MCV) values were 78.06±3.10 fL and 87.97±5.07 fL (p=0.034). The mean corpuscular hemoglobin concentration (MCHC) values were 29.90±0.62 g/dL and 32.62±1.77 g/dL (p=0.012). While 3 (100%) of 3 patients with ascending aneurysms survived, 6

(18.2) of 33 patients with descending aneurysm died (p=0.024, Table 3).

While 19 (54.2%) of 35 cases with aortic dissection in the study survived, 16 (45.8%) resulted in mortality. Thirty (83.3%) patients with aortic aneurysm survived, while 6 (16.6%) died (p=0.008, Table 4).

In the correlation analysis, there was a strong negative correlation between age and dissection, and a strong positive correlation between aneurysm. Additionally, both lactate and SI had a strong positive correlation with mortality (Table 5).

According to the ROC curve analysis of the patients, the optimal cut-off values of lactate and SI [area under the curve (AUC): 95% confidence interval (CI): 95%] to determine the positivity of dissection, aneurysm and mortality;

1. Dissection; Lactate: Sensitivity 77.1% and specificity 63.9%; (AUC; 0.700, 95% CI; 0.573-0.826, p=0.004). SI: Sensitivity 74.3% and specificity 61.3%; (AUC; 0.663, 95% CI; 0.534-0.793, p=0.018 (Figure 1).

Table 3. Relationship of variables with aortic dissection types

	Ascending mean ± SD		Descending mean ± SD	p value*
Age (year)	50.33±20.84		68.81±9.47	**0.001**
Lactate (mmol/L)	1.33±0.32		1.95±1.57	**0.013**
Shock index	0.58±0.03		0.63±0.15	0.056
Urea (mg/dL)	37.66±25.71		55.06±44.05	0.574
Creatinine (mg/dL)	0.76±0.32		1.49±1.41	0.312
Sodium (mmol/L)	133.66±8.50		140.65±5.66	0.386
Potassium (mmol/L)	4.22±0.78		4.23±0.70	0.769
WBC (×10³/mcL)	12.60±3.63		11.61±4.67	0.248
Hemoglobin (g/dL)	10.56±2.97		10.68±2.08	0.225
Hematocrit (%)	33.43±9.19		32.37±5.91	0.136
MCV (fL)	78.06±3.10		87.97±5.07	**0.034**
MCHC (g/dL)	29.90±0.62		32.62±1.77	**0.012**
PLT (×10³/mcL)	195.33±76.69		194.87±83.39	0.841
	n (%)		**n (%)**	**p value****
Mortality	**No**	3 (100)	27 (81.8)	**0.024**
	Yes	0 (0)	6 (18.2)	

*Mann-Whitney U test, **Chi-square analysis, WBC: White blood cell, MCV: Mean cell volume, MCHC: Mean corpuscular hemoglobin concentration, PLT: Platelet

Table 4. Mortality comparison in aortic dissection and aneurysm

		Dissection n (%)	Aneurysm n (%)	All patients n (%)	p value*
Mortality	**No**	19 (54.2)	30 (83.3)	49 (69.1)	0.132
	Yes	16 (43.8)	6 (16.6)	24 (30.9)	
Total		35 (100)	36 (100)	71 (100)	-

*Chi-square analysis

Table 5. Correlation analysis between variables

	Dissection		Aneurysm		Mortality	
	r	**p***	**r**	**p***	**r**	**p***
Gender	0.119	0.328	-0.196	0.101	0.194	0.105
Age	**-0.412**	**0.001**	**0.455**	**0.001**	0.047	0.694
Lactate	**0.279**	**0.019**	**-0.329**	**0.005**	**0.741**	**0.001**
Shock index	0.195	0.105	**-0.268**	**0.024**	**0.768**	**0.001**

*Spearman's rho analysis

2. Aneurysm; Lactate: Sensitivity 52.8% and specificity 48.6%; (AUC; 0.300, 95% CI; 0.174-0.427, p=0.004). SI: Sensitivity 47.2% and specificity 45.8%; (AUC; 0.337, 95% CI; 0.207-0.466, p=0.018 (Figure 2).

3. Mortality; Lactate: Sensitivity 98% and specificity 95.2%; (AUC; 0.968, 95% CI; 0.915-0.1020, p=0.001). SI: Sensitivity 96.7% and specificity 92.2%; (AUC; 0.980, 95% CI; 0.955-0.1005, p=0.001 (Figure 3).

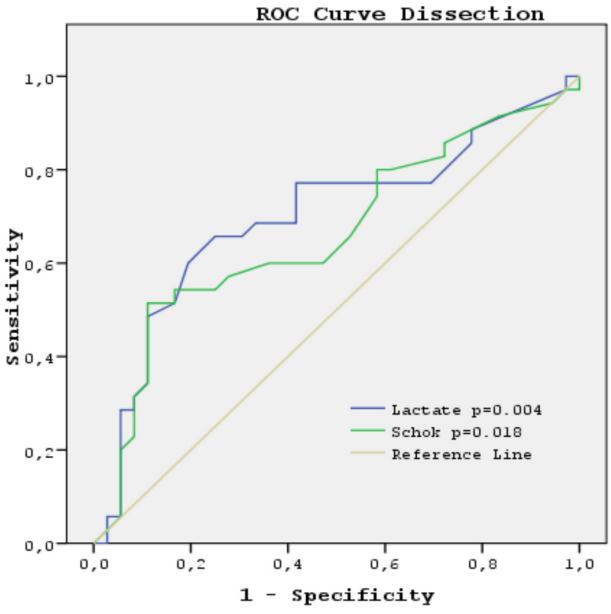

Figure 1. ROC curve analysis according to lactate V and shock index acute aortic dissection positivity

ROC: Receiver operating characteristic

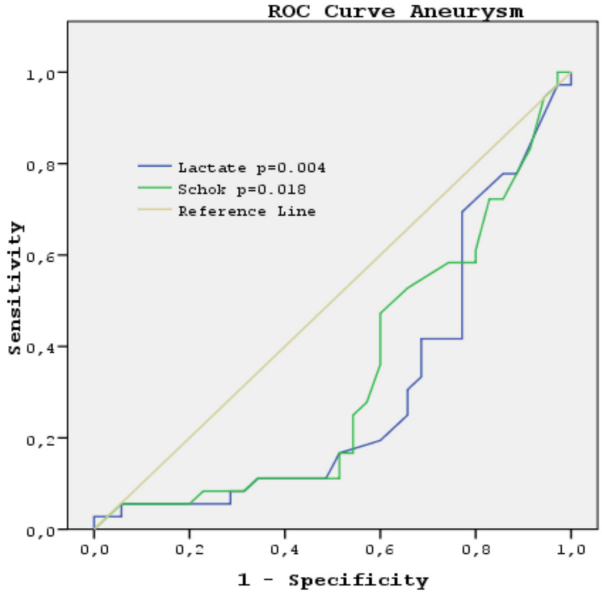

Figure 2. ROC curve analysis according to lactate V and shock index aortic aneurysm positivity

ROC: Receiver operating characteristic

Discussion

In aortic aneurysm and dissection, which is an important etiology for admission to emergency services, while seconds are so precious for the survival of the patient, providing faster and more practical approaches in diagnosis and treatment will bring the chance for rapid intervention and provide a significant reduction in morbidity and mortality.

Nutrition and oxygenation of the outer half of the aorta with the media layer are provided by vasa vasorums. Developing hypoxemia causes degeneration in the elastic structures in the tunica media, weakening the wall and paving the way for developing an aneurysm [8,9]. Aortic dissection results from a tear in the aortic intima because of pulsatile blood flow in the medial layer. Progressive separation of the aortic wall layer results in the formation of a false lumen, and re-entry into the true lumen via another intimal tear may also occur. This leads to rapid blood loss and death [10,11]. At the molecular level, aortic dissection is the result of remodeling of the aortic wall structure because of inflammation and extracellular matrix disruption. Activated macrophages infiltrate the tunica environment and release matrix metalloproteinases and proinflammatory cytokines [12].

Age is considered an independent factor in revealing vascular damage [13]. It is predicted that cardiovascular diseases will continue to be the leading cause of death in the greater than 65 age group. Aortic dissection is most common in this population

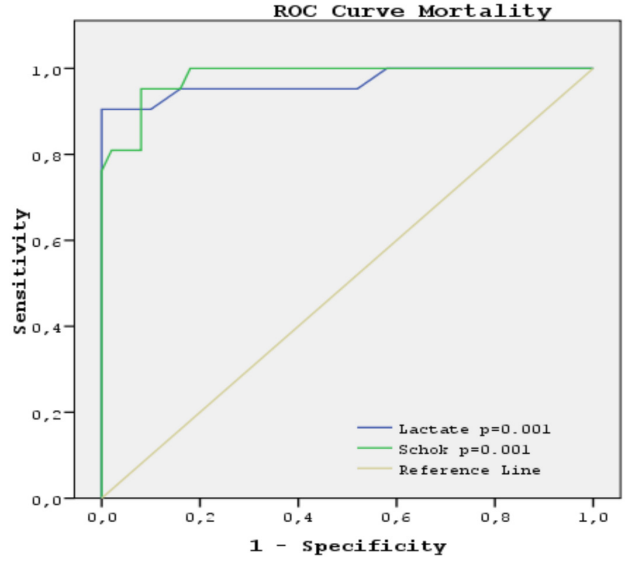

Figure 3. ROC curve analysis according to lactate V and shock index mortality positivity

ROC: Receiver operating characteristic

aged 65-75 years, with an incidence of 35 cases per 100,000 people per year [14]. The most important risk factor for its development is hypertension. Additionally, aortic dissection is seen 2-3 times more frequently in men than in women of the same age. The incidence of this disease under the age of 40 years is relatively rare, except family history, congenital heart diseases such as bicuspid aortic valve or aortic coarctation, Marfan syndrome, and pregnancy. In the literature, it is stated that the male/female ratio in relation to gender is 2-5/1. Again, in studies, it is seen more frequently in the age of 40-70 [2]. In the studies of Sbarouni et al. [15] it was reported that the mean age of patients with aortic dissection was 63±14 years, and the female/male ratio was 89/31. In our study, 56 (78.8%) of the patients were male and 15 (21.2%) were female. The mean age and gender distribution of our cases were similar to that of other studies.

In a study, hemogram values in dissection patients were evaluated whether they have any prognostic value in predicting hospitalizations and long-term mortality [16]. The MCV value makes a significant difference in the mortality rate in aortic dissection [17]. In the study by Hirst et al. [17] mortality was found to be higher in patients with distal type, malperfusion, or ruptured aortic dissection patients aged 70 and over. In our study, MCV and MCHC values in the patient group with ascending aortic aneurysm were found to be significantly higher in the patient group with descending aneurysm. This suggests that MCV and MCHC elevations may be indicators of both mortality and clinical severity.

Lactate level is a fast and easily accessible, safe parameter that increases especially in perfusion disorders. Lactate measurements in arterial blood gas can be used as a predictor of tissue hypoxia and metabolic acidosis after aortic dissection diagnosis. Serial lactate measurements may be useful in predicting mortality [18]. Lactate formation in body metabolism results from anaerobic glycolysis by causing bleeding, inadequate ventilation, hypovolemia, hypoxemia, and end-organ hypoperfusion following a traumatic injury [19,20]. Intense adrenergic discharge increases lactate formation in patients with acute bleeding [21]. In their study, Kruse et al. [22] suggested that the results obtained from blood lactate monitoring and especially serial lactate sampling in the risk assessment of patients admitted to the hospital acutely are valuable in predicting in-hospital mortality. This study recommended that all patients with lactate greater than 2.5 mmol/L at presentation require close clinical follow-up, and that serial lactate samples should be taken in patients with lower lactate levels [22]. The acute stage of vascular damage in the aorta and the extent of damage are related to lactate levels. In previous studies, it was observed that pulse fullness, heart rate, SBP, SI, O_2 saturation, and end-tidal CO_2 levels, which indicate end-organ perfusion, were correlated with plasma lactate levels [23-25]. The pain and/or stress experienced by patients with aortic dissection contribute to prehospital lactate levels. In a study conducted with 122 patients with aortic aneurysms, it was concluded that serum lactate levels were helpful in predicting mortality [26]. In another study conducted with 228 patients, it was concluded that one of the most important parameters determining the survival of patients in the perioperative period is serum lactate level [27]. In a study involving the cardiovascular system, Kawase et al. [28] investigated the effect of hospitalized blood lactate levels on early mortality in patients hospitalized with acute heart failure and found that SBP and HR were associated with early mortality. In our study, the lactate level was found to be 1.90±1.51 mmol/L and 3.22±2.09 mmol/L, respectively, in patients with aortic aneurysm or aortic dissection, and it was found to be useful in predicting mortality, and this elevation could also be interpreted as the effect of shock after dissection on the lactate level.

SI, which can be calculated from the patient's vital follow-up, is closely related to mortality. This index is an important parameter that can be calculated quickly and easily, without requiring additional laboratory results in patients, and helps in identifying critically ill patients in the emergency department. In the study by Hoff et al. [29], it was shown that acute aortic injury and mortality were associated with high SI. It is a critical clinical parameter that reflects changes in hemodynamics. According to literature reports, the SI is widely used in risk analysis for many diseases such as trauma, pulmonary embolism, severe pneumonia, and ectopic pregnancy [30]. In a study conducted with 313 patients with aortic aneurysms, it was shown that SI was directly related to mortality [31]. Studies have reported that an SI of 0.9 is an indicator of the risk of shock and even death for critically ill patients [32,33]. Mortality rates were found to be higher in patients with a SI of 0.97±0.54 than those with a SI of 0.52±0.12. It has been suggested that considering the SI is an important clinical indicator in the follow-up of patients with aortic dissection [34]. In our study, the shock indices of patients with type 1, type 2, and type 3 dissection were found to be 0.75±0.19, 0.64±0.19, and 0.66±0.13, respectively. It is thought that the SI may be a prognostic parameter in predicting mortality in patients with aortic aneurysm or dissection.

DeBakey type 1 was found most frequently in studies, followed by types 3 and type 2, respectively. In the study by Açıkalın et al. [35], type 1 dissection was observed in 10 of 22 patients, whereas type 1 dissection was detected in 13 of 14 patients with AAD in the study by Buket et al. [36]. In our study, 21 (60%) of 35 dissection patients were type 1 dissection and mortality was also significantly higher. Dissection types were at similar rates with other studies, and mortality was also significantly higher in type 1. Due to the increase in mortality, we believe

that all parameters we evaluated can give an idea about the types of aortic dissection, as well as be markers for mortality.

Despite advances in invasive diagnostic methods, AAD has high mortality. Accurate and rapid diagnosis can reduce the mortality rate below 50%. Although the mortality rate of the disease is 1% per hour for the first 24 h, particularly in dissections involving the ascending aorta, this rate reaches 75% at the end of the second week. In this respect, early diagnosis in these cases is an important factor that positively affects the prognosis [4]. In the study by Yeşilaras et al. [37], 89.4% of the patients were hospitalized, 2.1% died in the emergency room, and 8.5% were referred to another health institution. In the study by Sarıtaş et al. [38] no patients were hospitalized, 91.7% were referred to another health institution, and 8.3% died in the emergency room. In our study, 16 (43.8%) patients with dissection and 6 (16.6%) patients with aneurysm resulted in mortality. We attribute the fact that we have no patients transferred to another center and that our mortality rate is below 50%, because we are a tertiary healthcare institution.

With all these data, both lactate level and SI showed significant results in the relationship between aneurysm dissection and dissection types. Lactate and SI was high in type 1 dissection, and both parameters were found to be significantly higher in the aneurysm dissection relationship. We believe that their usability for diagnosis and classification will be clarified with additional studies.

Study Limitations

The limitations of the study include the single-center and retrospective nature of the study, difficulties in accessing the records, the lack of certainty that the registry represents all patients even though the participating researchers tried including all patients in their institutions, and the inability to fully evaluate the changes in the cause of death over time.

Conclusion

Although aortic dissection and aneurysm are not very common diseases in emergency services, they are among the real emergencies that require rapid diagnosis and treatment in terms of mortality. Emergency physicians should be careful about these diseases, which are uncommon but have very high mortality and should be careful about medical first treatment and consultation requests. Although the mean age of patients with aortic aneurysm is higher, the mortality after dissection is much higher. We think that lactate level and SI are important parameters in predicting mortality in aortic aneurysms and dissections, and prospective and multicenter studies are needed to ensure their practical use.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Helsinki Declaration of Human Research after the approval of the Health Sciences University, Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee (subject number: KAEK/2022.02.41, decision no: 41, date: 23.02.2022).

Informed Consent: All patients were informed, their consent was obtained for inclusion in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ç., Concept: H.Ç., A.C., B.D., Design: H.Ç., A.C., B.D., Data Collection or Processing: H.Ç., B.Ç., B.A., Analysis or Interpretation: A.C., B.D., B.Ç., B.A., Literature Search: H.Ç., A.C., B.D., B.Ç., Writing: H.Ç., B.D., B.Ç., B.A.

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

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ORIGINAL RESEARCH

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Analysis of Infection Factors According to the Results of Culture of Patients more than 65 Years Old, who Applied to University Affiliate 3rd Stage Hospital Emergency Department with Findings of Infection

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Abstract

Objective: Today, the elderly population is increasing and the emergency service applications are increasing for this reason. In elderly patients, infection findings are not specific as in younger patients, and atypical findings are more common in elderly patients. In this study, it was aimed to analyze the infectious agents detected in patients aged 65 and over who applied to the emergency department with signs or suspicion of infection and to draw attention to this issue.

Materials and Methods: Our study was planned as a single-center and retrospective observational study. Our study included 1,503 patients who were admitted to the emergency department between January 1, 2019 and January 1, 2020, and who met the study criteria, among whom infectious diseases were considered in the evaluation. The demographic, disease and outcome data of the patients were recorded. For statistical significance, $p<0.05$ was accepted as the significance level.

Results: In our study, 51.2% of 1,503 cases were male and 48.8% were female. The mean age of the cases was 76.45±7.49 years in men and 78.73±7.99 years in women. The most common reasons for admission were disordered general condition, abdominal pain and dyspnea; the most common foci of infection are pneumonia, urinary tract infection and biliary tract diseases, respectively; the most common infectious agents were *Escherichia coli*, *Streptococcus pneumoniae*, and methicillin-resistant *Staphylococcus aureus*, respectively. 70.1% of the cases were hospitalized in the ward, 22.4% in the intensive care units, and mortality was observed in 7.8% of the cases. Mortality was found to be higher in cases with *Pseudomonas auroginosa* and *Acinetobacter baumannii*.

Conclusion: It was determined that elderly patients came to the emergency department with more atypical complaints, they were at higher risk of mortality due to infection than younger patients, and resistant infectious agents were more common in these patients and caused mortality.

Keywords: Geriatrics, infectious, mortality, emergency

Introduction

Because of many important developments, such as the successes in the fight against infectious diseases, the point reached for treating diseases, and the improvement of living conditions, life expectancy at birth is increasing, and accordingly, the number of population in the world and in our country is increasing day by day. It is estimated that the world population will double in the next 20 years and that our country will become the most populous country in Europe in terms of elderly population 2050 [1]. With this increase in the elderly population, diseases seen in old age gain importance; infectious diseases also take their place in this context.

As we age, deformations occur in the anatomical structures of the human body. However, due to many factors such as aging in the immune system, increased comorbidity and nutritional problems, elderly people are predisposed to infectious diseases and inadequate responses is given to infections [2,3]. In the case of infection in elderly patients due to these reasons, rapid deterioration in the general clinical condition can be observed.

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In the elderly patient group, infection often progresses atypically and classic symptoms and signs of infection may not be present [4]. Falling or delirium may be the main finding of infection in elderly patients. Often, this patient group may present to the emergency services with atypical findings such as loss of appetite, weakness, falls, changes in consciousness, deterioration in daily activities and oral intake, confusion and delirium, rather than typical signs of infection. Organ failure that develops after community-acquired infections are seen at a higher rate in elderly patients than in younger patients.

Although fever is one of the main symptoms of infectious diseases, there may be no fever response even in severe infectious diseases in elderly patients. Again, this age group may present with atypical findings and complaints. Therefore, when evaluating the infection status in elderly patients, detailed anamnesis, comprehensive physical examination and laboratory evaluation should be performed and interpreted accurately [5].

All kinds of infections can be encountered in elderly patients. Many situations can occur within these species, from community-acquired infections to hospital infections [6]. These infections can be caused by bacterial, viral, fungal and parasitic origin. Urinary system infection, pneumonia, skin and soft tissue infections, gastroenteritis and post-invasive infections are common infections. Among these infections, the most common are urinary tract infection (28%), pneumonia (25%), and skin (18%) [7].

Infectious diseases are in the top 10 among the causes of hospitalization in patients over the age of 65, and in the top 5 among the causes of death over the age of 65. There is an increase in morbidity and mortality due to infectious diseases in this age group due to delays in diagnosis and treatment, weak immune response in elderly patients, and therefore the severe course of infections. In the literature, it is stated that infections play a role in 1/3 of deaths in the elderly and organ failure is more common than in young people [4].

In our study, it was aimed to analyze the infectious agents detected by culture results in patients aged 65 and over who applied to the Izmir Katip Celebi University, Ataturk Training and Research Hospital Emergency Service with the suspicion of infectious diseases, to reorganize empirical treatments considering these data, and to attract attention to this subject.

Materials and Methods

Study Design

Our study was conducted at a single center and was retrospective. The study was initiated after obtaining approval from the Izmir Katip Celebi University Local Ethics Committee of the hospital (decision no: 524, date: 09.01.2020). Patients admitted to Izmir Katip Celebi University, Ataturk Training and Research Hospital Emergency Service between January 1, 2019 and January 1, 2020 were retrospectively screened. Patients who were thought to have systemic infection findings after admission were included in the study. The automation system and emergency room patient files were reviewed and duplicate entries were excluded from the study.

Patient Selection

Patients admitted to our emergency department between January 1, 2019 and January 1, 2020 were identified. Cases were defined on the basis of the international diagnostic codes (International Statistical Classification of Diseases-10) in the automation system. Patients aged 65 and over who presented with signs of infection and had no missing data were included in the study. Patients whose data could not be accessed through the system and whose culture results could not be found were excluded from the study. One thousand seven hundred and eighty four patients who met the inclusion criteria were identified. Among these patients, 162 patients with missing data and 119 patients whose culture results could not be reached were excluded from the study. Among the remaining cases, the study was conducted with 1,503 patients.

Data Collection

A retrospective data analysis was performed in this study. The data were scanned through the hospital automation system and archive samples. Patients who met the inclusion and exclusion criteria were included in the study. The obtained data were recorded in the previously created study form. Demographic characteristics such as patient protocol numbers, names and surnames, gender, age; vital signs of patients (systolic blood pressure, diastolic blood pressure, pulse, fever); alanine transaminase (ALT), aspartate transaminase (AST), white blood cell (WBC), C-reactive protein (CRP) values, complete urinalysis results and factors determined in blood culture results were recorded from the tests taken at the emergency admission.

Statistical Analysis

Data were analyzed with SPSS Package Program version 20.0. Number, percentage, mean, standard deviation, median, minimum and maximum were used in the presentation of descriptive data. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test. Pearson chi-square test was used in the analysis of categorical variables. T-test was used to compare two independent numerical data and Kruskal-Wallis test was used to compare triple numerical data. $P<0.05$ was accepted as statistical significance level.

Results

A total of 1,503 patients were included in the study. 51.2% (n=770) of the cases were male and 48.8% (n=733) were female. The mean age of the cases was 77.56±7.82 (65-105)

years, the mean age in women was 78.73±7.99 (65-105) years, and the mean age in men was 76.45±7.49 (65-96) years were detected. The mean age was found to be significantly higher in female cases. There was no difference between the genders in laboratory values (Table 1).

The vital values of the patients were collected from the emergency cards in the digital data archive. Of the patients whose vital values were examined; mean systolic blood pressure 122.01±26.45 (59-240) mmHg, mean diastolic blood pressure 68.19±14.63 (30-120) mmHg, heart rate mean 94.23±33.99 (44-172) beats/min, mean temperature was 37.26±3.51 °C (35-40).

The laboratory values of the cases were created by collecting the data obtained from the examinations performed during their admission to the emergency department. In the blood tests of the cases; ALT mean value 32.28±6.24 U/I, AST mean value 33.85±6.94 U/I, mean CRP value 11.53±11.44 (0-93) mg/dL, and mean WBC 13 It was measured as 0.68±9.54 (0.40-134.0)x10^3/mm^3 (Table 1).

When the age, vital values and laboratory values of the cases were compared according to the outcomes; it was observed that the mean age of the patients hospitalized in the intensive care unit (ICU) was higher, but it was not statistically significant (Table 2).

It was observed that systolic blood pressure and diastolic blood pressure averages were higher in discharged patients, and the averages decreased as they went to the service and ICU, and this was statistically significant. Likewise, it was observed that the mean heart rate in the discharged patients was lower than the patients hospitalized in the service and ICU, and it was statistically significant. We observed that the mean fever value measured was higher in patients admitted to the ICU (Table 2).

It was observed that there was no statistically significant difference in the mean CRP levels between the cases. It was observed that ALT and AST values gradually increased from discharge to the patients who were admitted to the ICU. We observed that the mean WBC values of the cases hospitalized

Table 1. Distribution of numerical data means of the cases

Parameter	Mean ± SD	Minimum	Maximum	p*
Age (year)	77.56±7.82	65	105	
Female (year)	78.73±7.99	65	105	**<0.001**
Male (year)	76.45±7.49	65	96	
Systolic blood pressure (mmHg)	122.01±26.45	59	240	
Female (mmHg)	121.77±26.25	60	240	0.729
Male (mmHg)	122.25±26.66	59	220	
Diastolic blood pressure (mmHg)	68.19±14.63	30	120	
Female (mmHg)	68.23±14.48	30	114	0.930
Male (mmHg)	68.16±14.77	45	120	
Pulse (beats/min)	94.23±53.99	44	172	
Female (beats/min)	90.75±19.41	44	172	0.578
Male (beats/min)	91.31±19.78	44	170	
Fever (°C)	37.26±3.51	35.0	40.0	
Female (°C)	37.15±0.99	35.0	40.0	0.150
Male (°C)	37.23±0.98	35.0	39.8	
ALT				
Female (U/L)	31.75±5.95	6	461	0.345
Male (U/L)	32.58±6.63	8	528	
AST				
Female (U/L)	33.85±6.94	6	610	0.412
Male (U/L)	34.12±7.42	5	601	
CRP (mg/dL)	11.53±11.44	0	93.0	
Female (mg/dL)	11.37±11.47	0	90.7	0.610
Male (mg/dL)	11.68±11.41	0.1	93.0	
WBC (x10^3/mm^3)	13.68±9.54	0.40	134.0	
Female (x10^3/mm^3)	13.53±9.04	0.40	134.0	0.527
Male (x10^3/mm^3)	13.84±10.05	0.48	126.0	

*: Independent t-test used. SD: Standard deviation, CRP: C-reactive protein, WBC: White blood cell, ALT: Alanine transaminase, AST: Aspartate transaminase

in the ICU were higher than the other cases, but this situation was not statistically significant (Table 2).

When the distributions of the patients' age, vital values and laboratory values according to the mortality status were compared, it was calculated that the mean age was statistically significantly higher in the patients with a mortal course. We observed that the mean diastolic blood pressure was statistically significantly lower in mortal cases, and the averages of CRP and WBC values were significantly higher. There was no statistically significant difference between the groups in the mean values of systolic blood pressure, pulse, fever, ALT and AST (Table 3).

Chronic diseases of the cases were determined and collected from the automation system. The data obtained were analyzed and in our study, it was observed that 87% of the cases had at least one chronic disease; 54.4% had hypertension (HT), 49% had diabetes mellitus (DM), 20.2% had malignancy, 15.7% had congestive heart failure, 12.5% had chronic renal failure (CRF) and 39.1% had another chronic disease. Additionally, it was found statistically significant that mortality was higher in cases with malignancy and in those with another chronic disease.

In our study, the effects of chronic disease conditions on mortality were evaluated. In the cox regression analysis, it was observed that the presence of malignancy and a history of CRF in case of infection pose a statistical risk in terms of mortality in patients (p=0.001, p=0.014).

When the application complaints of the cases are examined; the most common complaint at presentation was general condition disorder (18.1%; n=272), the second most frequent were abdominal pain (13.5%; n=203) and the third most frequent were shortness of breath (12.2%; n=183). The relationship between admission complaints and mortality was examined, and it was seen that the highest mortality rate was in the patients who presented with headache, and this situation was statistically significant (Table 4).

When the infection foci detected because of the evaluation of the cases were examined; in the cases, pneumonia was the most common (38.5%; n=579), urinary system infection (23.7%; n=356) and biliary tract diseases (13.2%; n=198) were the third most frequent infections. appeared to be the focus. The distribution of other foci of infection is shown in Table 5. In the relationship between the foci of infection of the cases

Table 2. Age, vital values and laboratory values of the cases by outcome comparison

Parameter	Discharge Mean ± SD	Service admission Mean ± SD	ICU admission Mean ± SD	p*
Age (year)	77.51±7.08	77.30±7.92	78.39±7.45	0.063
Systolic blood pressure (mmHg)	129.64±17.44	123.69±26.49	117.55±28.27	**<0.001**
Diastolic blood pressure (mmHg)	71.41±11.43	69.08±14.12	64.32±16.36	**<0.001**
Pulse (beats/min)	89.65±16.27	94.34±62.71	95.44±24.67	**0.008**
Fever (°C)	37.25±0.89	37.02±2.02	38.03±6.44	**<0.001**
Lower (U/L)	26.14±7.25	30.14±7.12	39.14±10.64	**0.038**
AST (U/L)	28.36±6.28	28.24±7.54	36.71±8.98	**0.021**
CRP (mg/dL)	11.79±11.11	11.24±11.22	12.36±12.17	0.451

*: Independent t-test used. ICU: Intensive care unit, SD: Standard deviation, AST: Aspartate transaminase, CRP: C-reactive protein

Table 3. Comparison of age, vital values and laboratory values of the cases by mortality status

	Mortality		p*
Parameter	Survive Mean ± SD	Ex Mean ± SD	
Age (year)	77.29±7.79	80.74±7.52	**<0.001**
Systolic blood pressure (mmHg)	122.23±26.27	119.44±28.51	0.274
Diastolic blood pressure (mmHg)	68.42±14.52	65.48±15.62	**0.037**
Pulse (beats/min)	93.88±55.77	98.42±24.16	0.383
Fever (°C)	37.26±3.65	37.29 ±1.02	0.940
Lower (U/L)	32.88±8.24	33.12±7.78	0.785
AST (U/L)	33.25±6.78	33.81±7.25	0.540
CRP (mg/dL)	11.34±11.19	13.71±13.91	**0.032**
WBC (x10^3/mm^3)	12.85±7.75	23.58±18.85	**<0.001**

*: Independent t-test used. SD: Standard deviation, AST: Aspartate transaminase, CRP: C-reactive protein, WBC: White blood cell

and mortality: We observed that the most deaths were from pneumonia, followed by urinary system infections and biliary tract diseases. While mortality was observed in 7.8% (n=117) of the cases, no mortality was observed in 92.2% (n=1386) (Table 5).

While 7.5% (n=113) of the cases were discharged, 70.1% (n=1054) were followed up in the ward, and 22.4% (n=336) were hospitalized and treated in the ICU. Among the cases, the cases admitted to the ICU were mostly hospitalized with the diagnosis of pneumonia; it was observed that 91.4% of the cases with biliary tract diseases were hospitalized and more than half of the cases with upper respiratory tract infection were treated as outpatients (Table 6).

Only the patients who underwent blood culture analysis were included in our study and the results of the blood cultures were approved by a microbiology specialist. Because of the

Table 4. The relationship between admission complaints and mortality

	Mortality status		p
Application complaint	**Surviving cases n (%)**	**Exitus cases n (%)**	
General condition disorder	255 (93.8)	17 (6.2)	0.003
Stomach ache	186 (91.6)	17 (8.4)	0.003
Dyspnea	160 (87.4)	23 (12.6)	0.003
Fire	168 (92.3)	14 (7.7)	0.003
Blurring of consciousness	162 (90.0)	18 (10.0)	0.003
Cough	167 (93.3)	12 (6.7)	0.003
Nausea vomiting	65 (97.0)	2 (3.0)	0.003
Oral intake disorder	61 (98.4)	1 (1.6)	0.003
Dysuria	43 (95.6)	2 (4.4)	0.003
Weakness	31 (96.9)	1 (3.1)	0.003
Ileus	29 (96.7)	1 (3.3)	0.003
Diarrhea	23 (91.7)	2 (8.3)	0.003
Knee pain	23 (100.0)	0 (0,0)	0.003
Headache	11 (64.7)	6 (35.3)	0.003
Chest	2 (66.7)	1 (33.3)	0.003

Table 5. Foci of infection detected in the cases

	Mortality status		p
Infection focus	**n (%)**	**n (%)**	
Pneumonia	519 (89.6)	60 (10.4)	0.001
Urinary system infection	342 (96.1)	14 (3.9)	0.001
Bile tract diseases	185 (93.4)	13 (6.6)	0.001
Soft tissue infection	76 (93.8)	5 (6.2)	0.001
Intra-abdominal infection	34 (94.4)	2 (5.6)	0.001
Gastroenteritis	31 (100.0)	0 (0.0)	0.001
URTI	18 (100.0)	0 (0,0)	0.001
Central nervous system infection	8 (80.0)	2 (20.0)	0.001
Septic arthritis	9 (100.0)	0 (0.0)	0.001
Infective endocarditis	6 (100.0)	0 (0.0)	0.001
Catheter infection	6 (100.0)	0 (0.0)	0.001
Enterorectal fistula	2 (66.7)	1 (33.3)	0.001
Spontaneous bacterial peritonitis	2 (100.0)	0 (0.0)	0.001
Unknown	148 (88.1)	20 (11.9)	0.001
Total	1386 (92.2)	117 (7.8)	0.001

URTI: Upper respiratory tract infection

blood culture of the patients, the infectious agent was detected and in the results obtained; it was observed that there was no growth in 48.9% (n=736) of the cases, the result was considered contamination in 9.6% (n=144) and *Escherichia coli* in 8.2% (n=124) (n=122) *Streptococcus pneumoniae* was identified as the causative agent. Other infectious agents are given in Table 7.

Infectious agents detected because of culture and the mortality status of the cases were compared and the results are given in Table 7. When *Pseudomonas auroginosa* and *Acinetobacter baumannii* were detected among these factors, the mortality rate was found to be statistically significantly higher compared with other factors (p<0.001) (Table 7).

Discussion

As in the world, the elderly population and the dependency ratios of the elderly population are increasing in our country. Additionally, the proportion of the elderly population in admissions to the emergency department is increasing. Additionally, these patients apply to the emergency department with serious illnesses [8,9]. These patients have many comorbid diseases with atypical signs and symptoms that complicate the diagnosis and treatment. It often carries an increased risk of recurrent emergency admissions, hospitalization, and mortality [10]. Additionally, the outcome of these patients is associated with many conditions, such as functional status, comorbidity score, age, social support, multiple drug use, and cognitive impairment [11,12].

Elderly patients are often brought to emergency rooms by ambulance. These patients present to the emergency department with serious and more complex problems. Therefore, more radiological examinations and laboratory tests are performed on these patients. However, older patients stay in the emergency room for longer time [8,9,13]. These patients need 2.5-4.6 times hospitalization and 5 times intensive care hospitalization [10,14]. However, due to the high incidence of misdiagnosis in elderly patients, some of these patients are often discharged from the emergency room without being diagnosed or treated [10].

There is no specific training, such as approaching the geriatric patient in emergency residency training. For this reason, there are difficulties in the diagnosis and treatment of elderly patients [15,16]. However, the applications of these patients to the emergency department is increasing day by day. In our study, we analyzed the infectious agents in the blood culture results of elderly patients who applied to the emergency department with any suspicion of infection and to bring the information obtained to the literature.

In the literature, the rate of the elderly population in emergency service admissions varies between 12% and 50%. In a study by Satar et al. [17] in Turkey, this rate was found to be 12.3%. In the study by Ünsal et al. [18], this rate was found to be 12%. In our study, this rate was found to be 11.8% and it was evaluated as compatible with the literature. The difference in the rate of admission to the emergency service of elderly patients may vary according to the country, city, region and the elderly population in that region.

Table 6. Distribution of outcome status of the cases by infecti

	ICU	Ward	Discharge	p
	Outcome			
Infection focal	**n (%)**	**n (%)**	**n (%)**	
Pneumonia	176 (30.4)	371 (64.1)	32 (5.5)	<0.001
Urinary system infection	66 (18.5)	244 (68.5)	46 (12.9)	<0.001
Bile tract diseases	17 (8.6)	181 (91.4)	0 (0.0)	<0.001
Soft tissue infection	18 (22.2)	57 (70.4)	6 (7.4)	<0.001
Intra-abdominal infection	8 (22.2)	28 (77.8)	0 (0.0)	<0.001
Gastroenteritis	6 (19.4)	21 (67.7)	4 (12.9)	<0.001
URTI	0 (0.0)	8 (44.4)	10 (55.6)	<0.001
Central nervous system infection	3 (30.0)	7 (70.0)	0 (0.0)	<0.001
Septic arthritis	-	5 (55.6)	4 (44.4)	<0.001
Infective endocarditis	3 (50.0)	3 (50.09)	0 (0.0)	<0.001
Catheter infection	3 (50.0)	3 (50.09)	0 (0.0)	<0.001
Enterorectal fistula	3 (100.0)	0 (0.0)	0 (0.0)	<0.001
Spontaneous bacterial peritonitis	0 (0.0)	2 (100.0)	0 (0.0)	<0.001
Unknown	33 (19.6)	124 (73.89)	11 (6.5)	<0.001

Biliary tract diseases: Includes acute cholangitis, acute pancreatitis and acute cholecystitis. URTI: Upper respiratory tract infection, ICU: Intensive care unit

In the literature, it has been determined that women aged 65 and over apply to the emergency service at a higher rate [18-20]. In the study of Lim and Yap [21], it was reported that 56% of patients aged 65 and over who applied to the emergency department were male. In our study, similar to the findings of Lim and Yap [21], 51.2% of male patients aged 65 and over applied more frequently. It was thought that this rate, which was determined differently from the literature, may be due to the characteristics of the region and because men are given more value due to the patriarchal family structure in our country. It is also effective for men to apply to the emergency room for even the smallest thing. In women, we thought that it might be due to more hesitation in going to the hospital or the emergency room.

With increasing age, some diseases may occur because of naturally occurring physiological changes. Therefore, the prevalence of chronic disease in elderly patients is higher than in younger patients. Özdemir et al. [22] reported that patients over 65 years of age with at least one chronic disease constitute 79% of all patients over 65 years of age. In a study by Fadıloğlu and Tokem [23] in our country; it was reported that 90% of patients aged 65 and have a chronic disease, 35% have two chronic diseases and 23% have three chronic diseases. In our study, it was observed that 87% of the cases had at least one chronic disease; it was determined that HT was the most common with a rate of 54.4%, and DM was the second most common with a rate of 49%. Additionally, the presence of these diseases has a positive effect on mortality. In the cox regression analysis performed in our study, it was observed that malignancy and CRF increased mortality statistically significantly.

Complaints on admission to hospital in elderly patients are often atypical complaints [4,5]. In the literature, it has been reported that non-specific findings such as falling, mental status changes, delirium, urinary incontinence and fatigue are common causes of presentation in elderly patients [24,25]. In their study, Norman and Toledo [26] stated that one of the important reasons for their atypical presentations is underlying chronic diseases. In the study of Temel and Akçam [2], it was reported that they are most frequently applied due to fever, cough, sputum, and confusion. In our study, it was observed that the most frequent complaints were general condition disorder, abdominal pain and shortness of breath, respectively. We think that these differences in the frequency of admission

Table 7. Comparison of the effects of infectious factors on mortality in the cases

	Mortality atatus		p*
Culture factor result	**No n (%)**	**Yes n (%)**	
No reproduction	704 (95.7)	32 (4.3)	<0.001
Contamination	129 (89.6)	15 (10.4)	<0.001
Escherichia coli	118 (95.1)	6 (4.9)	<0.001
Streptococcus pneumoniae	110 (90.2)	12 (9.8)	<0.001
MRSA	90 (87.4)	13 (12.6)	<0.001
Staphylococcus aureus	84 (93.3)	6 (6.7)	<0.001
Klebsiella pneumoniae	41 (87.2)	6 (12.8)	<0.001
Enterococcus faecalis	42 (89.4)	5 (10.6)	<0.001
Acinetobacter baumannii	26 (74.3)	9 (25.7)	<0.001
Pseudomonas aeruginosa	7 (58.3)	5 (41.7)	<0.001
Staphylococcus haemolyticus	9 (75.0)	3 (25.0)	<0.001
Staphylococcus epidermidis	8 (100.0)	0 (0.0)	<0.001
Aerococcus species	5 (83.3)	1 (16.7)	<0.001
Candida albicans	5 (83.3)	1 (16.7)	<0.001
Candida glabrata	5 (83.3)	1 (16.7)	<0.001
Staphylococcus lugdunensis	6 (100.0)	0 (0.0)	<0.001
Enterococcus raffinosus	5 (83.3)	1 (16.7)	<0.001
Gram (+) basil	5 (83.3)	1 (16.7)	<0.001
Streptococcus spp.	6 (100.0)	0 (0.0)	<0.001
Streptococcus pyogenes	6 (100.0)	0 (0.0)	<0.001
Yeast mushroom	5 (83.3)	1 (16.7)	<0.001

*: Fisher's Exact test used, MRSA: Methicillin-resistant *Staphylococcus aureus*

complaints in the literature are due to the differences in sociocultural levels, socioeconomic levels and existing chronic diseases in the regions where the hospitals are located.

Although there are serious bacterial infections in the elderly, there may still be applications with normal body temperature. The reason for this is the functional disorders seen due to aging. Although the presence of fever suggests infection, its absence does not exclude it [27,28]. This may cause delays in diagnosis in some infective diseases. As a result, mortality and morbidity in patients increase [29-31]. In the study of Gleckman and Hibert [32], fever was reported in only 13% of patients with bacteremia. Similarly, in the study of Castle et al. [33], fever was found in only one-third of the elderly patients with infection. In our study, fever was observed in 32.4% of the cases, and it was found to be compatible with the literature.

The arrival vital values of the cases were evaluated and when the obtained results were examined; it was observed that when the severity of the patients increased (from discharge to intensive care), there was an increase in the mean pulse rate and a decrease in systolic and diastolic blood pressure values. This explains the emergence of sepsis and septic shock findings in patients with intense infection. A comparison could not be made due to the absence of similar studies in the literature.

In the diagnosis of infection in elderly patients, tests such as leukocytes and CRP are studied. Laboratory findings of elderly patients may differ from those of younger patients. The leukocyte increase in the complete blood count may have been lower than expected. Studies have shown that there is no increase in white blood cells a serious infection in geriatric patients with a frequency of 32%-49% [1]. In the study of Bentley et al. [34], they associated the higher leukocyte count in geriatric patients with the presence of a bacterial infection. In our study, CRP and leukocyte values were found to be statistically significantly higher in cases with mortality. Additionally, in the cox regression analysis performed, it was observed that statistically significant mortality was also high in cases with increased leukocyte levels, but no such relationship was found between CRP and mortality.

In our study, the most common focus of infection was pneumonia, the second most common urinary tract infections, and the third most common biliary tract diseases. Uluğ et al. [35] evaluated community-acquired infections in elderly patients and found that pneumonia and acute gastroenteritis were the most common causes, respectively. Avkan-Oğuz et al. [36] reported that urinary system infections, acute gastroenteritis and pneumonia were the most common foci of infection in elderly patients, respectively. As in these studies, urinary tract infections and pneumonia are the most common focus of infection in geriatric patients, and our study was found to be compatible with the literature. We think that this situation arises due to the need for care of elderly patients and the inability to perform self-hygiene.

The causative microorganisms in infectious diseases differ among young populations depending on the place where the infection is acquired (community origin, nursing home) and accompanying diseases [35]. In the study of Temel and Akçam [2], the most common agents in elderly patients were *E. coli* (36%), *Brucella* spp. (3%) and *Acinetobacter* spp. (3%) was found [24].

In our study, blood culture samples were taken from 1503 patients and no growth was observed in 48.9% (n=736) of these samples; *E. coli* (8.2%) was the most common infectious agent, *S. pneumoniae* (8.1%) was the second most common and methicillin-resistant *Staphylococcus aureus* (MRSA) was the third (6.7%). In addition, it should be considered that resistant agents such as MRSA (6.7%), *Acinetobacter* (2.3%), *P. aeroginosa* (0.8%) are more common in the elderly. Our study was found to be similar to the literature. The reason for the high number of cases with no growth in culture; it was thought that viral infections could be seen frequently or inappropriate culture cultivation.

The effect of the infectious agents detected in the cases on mortality was examined and it was observed that resistant infectious agents such as *P. aeroginosa* (41.7%) and *A. baumannii* (25.7%) caused the highest mortality. This situation shows us that if resistant infectious agents are detected in elderly patients, treatment should be started quickly and close follow-up should be done.

Conclusion

In our study, it should be kept in mind that elderly patients presenting with signs of infection may have a resistant infection, early blood culture should be taken, treatment should be started quickly, and close follow-up should be performed. It should be kept in mind that especially patients with a history of malignancy and CRF are at risk of mortality. We have seen that the most common focus of infection is pneumonia and urinary system infection, and therefore we think that social education and hygiene measures will reduce both the mortality in geriatric patients with infectious diseases and the losses in our country's economy.

Ethics

Ethics Committee Approval: Izmir Katip Celebi University Local Ethics Committee of the hospital (decision no: 524, date: 09.01.2020).

Informed Consent: A signed voluntary consent form was obtained from all patients included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.D., U.P., S.B., Concept: A.K., M.G.E., S.B., Design: U.P., A.K., M.G.E., S.B., Data Collection or Processing: E.D., M.G.E., S.B., Analysis or Interpretation: E.D., U.P., A.K., Literature Search: E.D., U.P., A.K., S.B., Writing: E.D., U.P., M.G.E.

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ORIGINAL RESEARCH

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The Rate of Influenza and Respiratory Syncytial Virus in Patients with Upper Respiratory Infection Symptoms During the COVID-19 Pandemic Period

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Abstract

Objective: This study investigates the rates of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) influenza and respiratory syncytial virus (RSV) in patients who presented to the emergency department with symptoms of upper and lower respiratory tract infections during the coronavirus disease-2019 (COVID-19) pandemic.

Materials and Methods: This study was conducted on patients admitted to the University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital, Clinic of Emergency with symptoms of upper respiratory tract infection between 15.03.2021 and 15.05.2021. SARS-CoV-2 and RSV were studied using multiplex polymerase chain reaction (PCR) test on nasopharyngeal swab samples taken from these patients. The research was conducted as a prospective, descriptive case study. Patient selection was determined by physicians working in green area polyclinics. The samples are taken in the "COVID-19 PCR sample collection area of our hospital". Two nasopharyngeal swabs were taken from all patients.

Results: A total of 359 patients participated in this study. Of these patients, 51% were men and 49% were women. The age range of these patients ranged from 17 to 70, with a mean age of 36.2. Three hundred forty nine of these patients followed up as outpatients. Of the patients,71.3% included in our study had no history of comorbid disease. SARS-CoV-2 was positive in 94 of the patients participating in our study. Cough, shortness of breath, wheezing and fever were found to be significantly higher in SARS-CoV-2 patients, however nasal discharge was significantly higher in the group with patients had not SARS-CoV-2.

Conclusion: Measures taken against the transmission of SARS-CoV-2 during the pandemic period also reduced the incidence of other respiratory viruses. Historical declines have been found in the influenza and RSV ranks. When the restrictions are lifted, epidemics from other respiratory viruses are also expected. Surveillance studies of these viruses should be closely followed and should be prepared for new outbreaks.

Keywords: SARS-CoV-2, influenza, RSV, multiplex, RT-PCR

Introduction

Coronavirus disease-2019 (COVID-19) illness is a highly infectious respiratory disease that initially surfaced in Wuhan, China, in December of this year and has spread around the world. On February 11, 2020, the World Health Organization (WHO) issued a definition for it [1]. The most common symptoms are fever, coughing, shortness of breath, muscular and body pains, and fatigue.

The virus that causes COVID-19 illnesses is severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which is a member of the Coronaviridae family. İt was discovered on January 7, 2020, and the virus's name has been provisionally designated as 2019-new cooperative virus [2]. On February 11, 2020, the WHO issued a definition for it [1]. Acute respiratory distress syndrome (ARDS) is the most serious consequence in patients with severe illness, and it may develop as soon as the beginning of dyspnea has been seen in the patient. Studies

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have indicated that on average, it takes 8 days from the onset of symptoms to develop ARDS [3].

Influenza viruses are members of the orthomyxoviridae family of viruses [4]. Viruses of this size (80-120 nm in diameter) are enclosed RNA viruses with helical nucleocapsids and RNA genomes [5]. There are four separate influenza strains (types A, B, and C), each with its own set of antigenic characteristics, as well as a fourth kind (D) that has just recently been discovered [6]. Influenza A and B are the types of influenza that are most often associated with sickness in humans. Influenza is a disease that affects people of all ages. Pregnant women, children under 5 years old, the elderly, those with chronic conditions, and those using immunosuppressive medications are among the most at risk, since they are at greater risk of developing more severe disease and complications. Influenza A viruses in particular can cause pandemics due to the exchange of components between two distinct viruses that infect the same cell (a process known as antigenic shift). When it comes to pediatric populations, respiratory syncytial virus (RSV) is a major source of respiratory illness worldwide. After an RSV infection, there is no development of permanent immunity, and the virus may be transmitted throughout one's life [7]. When it comes to persons over 50 years of age with underlying illness, it is a significant and difficult to identify the cause of lower respiratory tract infection (LRTI). Among adults over the age of 50, prospective research found that the yearly hospitalization rate for RSV was 15 per 10,000 people [8]. Over the age of 50, a 6%-8% death rate was seen among people admitted to the hospital with respiratory RSV [9]. Pediatric lower respiratory tract illness (bronchospasm, bronchiolitis, pneumonia, acute respiratory failure) and apnea are common in newborns who have contracted the virus via their mother's breast milk. In newborns with RSV infection, wheezing is evident in 20% of cases, and 2%-3% need inpatient treatment [10].

While the COVID-19 pandemic was underway, this research aimed to determine the prevalence of SARS-CoV-2, influenza, and RSV in patients who presented to the emergency room with symptoms of upper and lower respiratory tract illnesses.

Materials and Methods

Design and Settings

An exploratory, descriptive case study design was used in our research. The study was conducted in polyclinics of University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital, Emergency Service between March 15, 2021 and May 15, 2021. University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital Local Ethics Committee was appropriated the study (rulling number: 514/196/21). When patients with upper respiratory tract infection presented with symptoms, nasal swab samples were obtained and tested for the presence of SARS-CoV-2, influenza, and RSV agents using a multiplex polymerase chain reaction (PCR) assay. They were collected at our hospital's "COVID-19 PCR sample collection area," which was designated for this purpose. On average, every patient had two nasopharyngeal swabs collected. Using the first, we could create an RV2 panel, while using the second, we could create our hospital's standard COVID-PCR test.

Participants

The inclusion criteria for this study included at least oa symptomof upper and LRTIs, such as rhinorrhoea, cough, shortness of breath, sore throat, coughing, fever, muscle and joint discomfort, loss of taste and smell, weakness, and being above the age of 18. Patients under the age of 18 who did not match the inclusion criteria, as well as those who had been to the emergency department with the same complaint within the previous seven days, were omitted from the research.

Data Collection and Processing

Following the entry of the patients' demographic information, the data form was also used to record their blood pressure, temperature, pulse, respiration rate, and the results of their physical examination. Patients with suspected COVID-19 infection who present to the emergency room are typically given a nasopharyngeal swab sample. The patients also had a second sample taken from their nose and placed into virus transport medium (VTM) tubes, which were then transported to the emergency microbiology laboratory during the day without the need to wait and stored at -80 °C in a Nuve 590 deep freezer, which was specifically purchased for our study. After the samples were thawed from the deep freeze on the day of the analysis, 50 mL of sample was extracted from the sample and 50 mL viral RNA extraction solution buffer for nucleic acid extraction was transferred to a PCR tube for further analysis. Incubation took place at room temperature for 5 min after being pipetted and mixed up and down five times. One hundred microliters of the mixture were made. By vortexing and mixing the PCR tubes, it was possible to swiftly centrifuge them. According to the Biorad CFX96 parameters, measurements were initiated after one cycle of 10 min at 50 °C, one cycle of 2 min at 95 °C, and one second at 95 °C and 60 °C, respectively. Bio-RAD company's CFX96 *in vitro* diagnostics real time-PCR instrument was utilized in this investigation. The causal culprit was identified using the GeneMAP respiratory viral PCR panel 2 test from the Genmark firm. A nasopharyngeal swab was used to collect samples, which were then transferred to the VTMs.

Outcome Measures

As the main endpoint of this research, we will look at the incidence of SARS-CoV-2, influenza, and the number of patients who presented to the emergency department with symptoms of upper and LRTIs during the COVID-19 pandemic period.

Statistical Analysis

SPSS 19.0 for Windows was used to conduct the statistical analyses. In the percentage distribution of descriptive criteria, the mean and standard deviation, the median and the minimum-maximum values are displayed as percentages. Kolmogorov-Smirnov test was used to determine if the data conformed to the normal distribution. When comparing distributions across groups, the chi-square test was employed, and when comparing continuous variables, the Student's t-test was used. It was decided that $p<0.05$ would be the threshold of significance.

Results

Three hundred and fifty nine patients were included in the study. Males accounted for 183 (51% of the total) of the patients, with female accounting for 176 (49%). A positive SARS-CoV-2 test resulted in 44 (12.25%) of the male patients, whereas the test resulted in 139 (38.7%) of male patients. In our hospital's COVID-19 PCR findings, SARS-CoV-2 was positive in 88 patients (24.5%) and SARS-CoV-2 was negative in 271 patients, according to the results of the COVID-19 tests. According to our findings, 94 (26.2%) patients had positive SARS-CoV-2 tests, whereas 265 (73.8%) had negative test results. Although 13 patients were found to be positive on respiratory viral PCR panel 2, they were found to be negative according to the COVID-19 PCR results, and on the other hand, 7 patients were found to be positive according to the COVID-19 PCR results but negative on respiratory viral PCR panel 2, indicating that the COVID-19 PCR results were unreliable. Table 1 presents a graphical representation of the distribution of additional illnesses based on PCR data obtained from individuals who took part in the study. Following this pattern, cardiovascular illness was shown to be the comorbidity that was most often related to PCR positive. Patients' clinical results are presented in Table 2 as well as the characteristics of the patients. Table 3 summarizes the findings of the respiratory viral PCR panel 2 and the COVID-19 PCR tests that were conducted at our institution. No patients were detected infected with RSV or influenza.

Discussion

A total of more than 200 viruses and viral subtypes have been identified as causing upper respiratory tract infections. Infections of the upper respiratory tract are caused by several different pathogens including coronaviruses (coronaviruses), influenza (flu), parainfluenza (parainfluenza) (rsv), rhinoviruses (rhinoviruses), metopnomovirus (metopnomoviruses), bocavirus (bocavirus) and adenovirus. Although they generate non-life threatening symptoms such as rhinorrhoea and sore throat, most these infections are self-limiting and clear within a week or less. Since LRTIs are associated with significant morbidity and death, early and prompt diagnosis and treatment are essential. Lung infections are mainly caused by viruses such as influenza, rhinoviruses (shingles), human metapneumoviruses, and parainfluenza viruses. Other reasons

Table 1. Examination of the distribution of chronic disease characteristics in the positive and negative groups according to the PCR results

Variabels	Absent/present	Negative (n=265)		SARS-CoV-2 (n=94)		Total	Sig.
		n	%	n	%	n	p
Cardiovascular disease	Absent	256	96.6	84	89.4	340	**0.007**
	Present	9	3.4	10	10.6	19	
Hypertension	Absent	243	91.7	79	84.0	322	**0.04**
	Present	22	8.3	15	16.0	37	
Diabetes mellitus	Absent	253	95.5	81	86.2	334	**0.002**
	Present	12	4.5	13	13.8	25	
Chronic renal failure	Absent	262	99.2	94	100.0	356	0.39
	Present	2	0.8	0	0.0	2	
Malignancy	Absent	260	98.5	93	98.9	353	0.75
	Present	4	1.5	1	1.1	5	
Chronic lung disease	Absent	255	96.2	89	94.7	344	0.52
	Present	10	3.8	5	5.3	15	
Cerebrovascular disease	Absent	264	99.6	94	100	358	0.55
	Present	1	0.4	0	0.0	1	
Other	Absent	227	85.7	67	71.3	294	**0.002**
	Present	38	14.3	27	28.7	65	

PCR: Polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

may also cause lung involvement, although they are far less common. Because RSV and influenza (flu) create seasonal epidemics, they are associated with significant increases in hospitalizations, as well as significant morbidity and death, particularly during the winter. RSV and influenza were found to be the most frequent respiratory viruses, according to research conducted at Ege University in 2015. The study measured the incidence of respiratory viruses between 2002 and 2014 [11].

According to a review of the literature, research conducted on 250 patients to identify co-infected individuals between 19 January and February 26, 2020 at the beginning of the pandemic period revealed that 30 (15.6%) of 250 patients tested positive for at least one respiratory tract infection [12]. It was discovered that the frequencies of influenza and parainfluenza had reduced dramatically in research conducted in Texas between 11 and 23 and 2020 in the latter

Table 2. Examination of the distribution of clinical signs and features in SARS-CoV-2 positive and negative groups

Variables	Absent/present	Negative (n=265)		SARS-CoV-2 (n=94)		Total	Sig.
		n	%	n	%	n	p
Cough	Absent	139	52.5	30	31.9	169	**0.001**
	Present	126	47.5	64	68.1	190	
Shortness of breath	Absent	240	90.6	77	81.9	317	**0.03**
	Present	25	9.4	17	18.1	42	
Throatache	Absent	95	35.8	44	46.8	139	0.06
	Present	170	64.2	50	53.2	220	
Grunt	Absent	258	97.4	86	91.5	344	**0.02**
	Present	7	2.6	8	8.5	15	
Fever/chills	Absent	202	76.2	50	53.2	252	**0.001**
	Present	63	23.8	44	46.8	107	
Tiredness	Absent	148	55.8	51	54.3	199	0.79
	Present	117	44.2	43	45.7	160	
Headache	Absent	189	71.3	62	66.0	251	0.33
	Present	76	28.7	32	34.0	108	
Muscle and body pain	Absent	141	53.2	46	48.9	187	0.48
	Present	124	46.8	48	51.1	172	
Loss of taste and odor	Absent	250	94.3	83	88.3	333	0.05
	Present	15	5.7	11	11.7	26	
Diarrhea	Absent	253	96.2	90	95.7	343	0.85
	Present	10	3.8	4	4.3	14	
Nausea	Absent	247	93.6	88	93.6	335	0.99
	Present	17	6.4	6	6.4	23	
Sneeze	Absent	224	84.8	83	89.2	307	0.29
	Present	40	15.2	10	10.8	50	

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

Table 3. Comparison of respiratory viral PCR panel 2 and COVID-19 PCR results performed in our hospital

			COVID-19 PCR		Total
			Negative	Positive	
Respiratory viral PCR panel 2	Negative	Count	258	7	265
		% of total	71.9	1.9	73.8
	SARS-CoV-2	Count	13	81	94
		% of total	3.6	22.6	26.2
Total		Count	271	88	359
		% of total	75.5	24.5	100.0

PCR: Polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COVID-19: Coronavirus disease-2019

phases of the pandemic, and that coinfection had not been detected in 262 SARS-CoV-2-positive individuals throughout the study period [13]. According to surveillance tests done in Australia between March and September 2020, influenza and RSV agents were found to have fallen considerably compared to the previous year's figures [14]. Nine hundred two of 6,079 individuals who applied for COVID-19 were tested for influenza at the same time in a trial conducted in New York; just three patients were found to have co-infection [15]. Approximately 269,303 samples were analyzed between May 10 and May 23 by global influenza surveillance and response system labs in 89 countries associated with the WHO. Influenza was discovered in 484 (0.17%) of the samples tested [16]. According to WHO statistics broken down by year, the number of cases in January in prior years was 60,000 per week. This season's total number of cases was assessed to be 484 [17]. Figure 1 depicts the graphs examining the effects of viruses by year in the report of changes in influenza and other respiratory tract

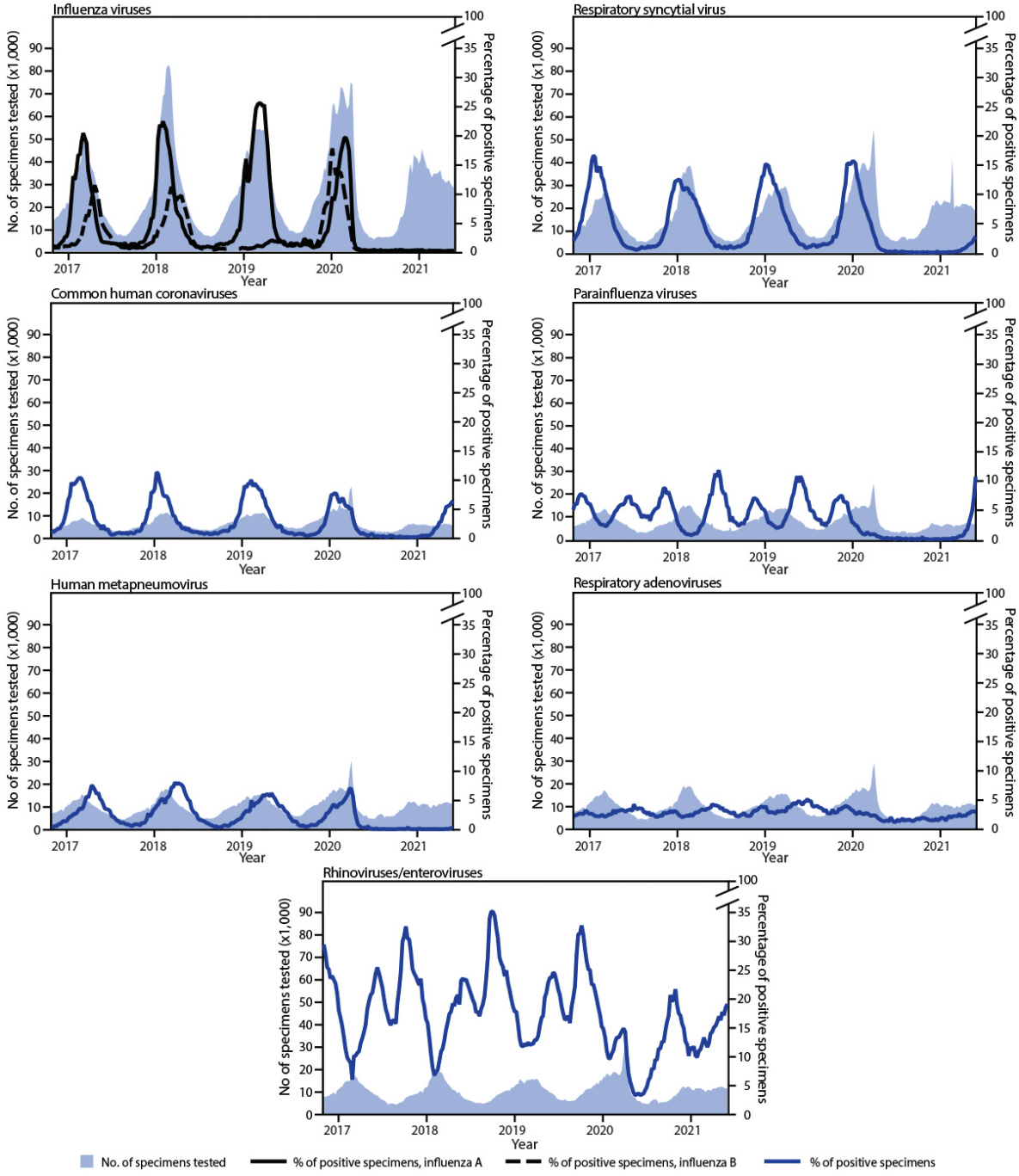

Figure 1. Changes in MMWR influenza and other respiratory viruses by year

MMWR: Mortality and morbidity weekly report

virus activity in the COVID-19 pandemic published in the CDC mortality and morbidity weekly report published on July 23, 2021 and examining the effects of viruses in the report of changes in influenza and other respiratory tract virus activities in the COVID-19 pandemic.

In our investigation, there were certain limitations. The fact that this is a single-center study with a limited sample size, as well as the small number of patients who tested positive for influenza and RSV, are all significant limitations of the study.

Conclusion

It was discovered that no patients had been infected with influenza or RSV throughout our research. Although it can make a methodological contribution to the new studies, it also can push the notion of pandemia-on-pandemia to the forefront of the discussion in the literature.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital Local Ethics Committee was appropriated the study (rulling number: 514/196/21).

Informed Consent: Prospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., Ö.T., İ.T., A.U.S., E.Y., R.A., N.M.H., Concept: M.A., Ö.T., A.U.S., R.A., Design: M.A., Ö.T., İ.T., N.M.H., Data Collection or Processing: M.A., Ö.T., E.Y., E.K., Analysis or Interpretation: Ö.T., R.A., N.H., Literature Search: M.A., İ.T., R.A., Writing: N.H., Ö.T., A.U.S., E.Y.

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CASE REPORT

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A Rare Case of Mortal Metformin Intoxication

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Abstract

Metformin is the first-line oral antidiabetic for treating type 2 diabetes mellitus (DM). Its major toxicity is lactic acidosis (LA). Metformin-induced LA (MILA) rarely develops in the absence of an acute overdose. However, LA is the most serious complication of metformin intoxication, and MILA is associated with high mortality rates. We presented a comparative evaluation of a mortal MILA case with the literature. A 47-year-old woman with type 2 DM and using metformin, admitted to the emergency department with abdominal pain and vomiting that started 4 h after taking 60 gr metformin for suicide. There was no abnormality on her initial hemogram, biochemical profile, or coagulation findings. However, her arterial blood gas analysis on admission was remarkable for pH: 7.025 and lactate: 20.32 mmol/L. HD was planned rapidly in the patient with high anion gap metabolic acidosis. Despite the aggressive therapy, the patient developed ventricular fibrillation and then cardiac arrest and died in the 4th hour of her admission to the emergency department. Under acute and high-dose metformin intoxication, metabolic acidosis can develop rapidly. Hemodialysis therapy should not be delayed, particularly in cases with MILA. It should be remembered that these cases are mortal despite aggressive treatment.

Keywords: Hemodialysis, lactic acidosis, metformin, mortality, suicide

Introduction

Metformin is the first-line oral antidiabetic for treating type 2 diabetes mellitus (DM) [1]. Although metformin is an antihyperglycemic agent, it does not induce hypoglycemia in a single-use [2]. It may cause kidney or hepatic insufficiency above the therapeutic dose, but its major toxicity is lactic acidosis (LA) [3]. Metformin-induced LA (MILA) rarely develops in the absence of acute overdose [4]. However, LA is the most serious complication of metformin intoxication, and MILA is associated with high mortality rates. Lalau and Race [5] reported a mortality rate of 45% in their case series of 49 metformin-treated and developed LA patients. In Vecchio et al.'s [6] case series consisting of 66 patients, the mortality rate was 26%.

We evaluated a rare case of metformin intoxication developed LA after drug overuse and resulted in death in a short time after the first admission to the emergency department.

Case Report

A 47-year-old woman with type 2 DM and using metformin, admitted to the emergency department with abdominal pain and vomiting that started 4 h after taking 60 tablets of 1000 mg metformin (60 g) for suicide. Her general condition became moderate upon admission. She was conscious and oriented, with a Glasgow Coma scale of 15/15. Vital signs were stable; blood pressure was 100/60 mmHg, pulse 110/min, respiratory rate was 20/min, and SpO_2 was 98% on room air. On physical examination, her pupils were isochoric and reactive. Except for tachycardia, no abnormality was detected on heart and chest examination. She had diffuse abdominal tenderness; however, there was no defense or rebound on abdominal examination. After the gastric lavage and activated coal (1 gr/kg) therapy, hydration with 0.9% isotonic NaCl and symptomatic treatment was started. There was no abnormality on her initial hemogram, liver function tests (aspartate aminotransferase, alanine transferase), blood urea nitrogen, creatinine, electrolyte values,

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Table 1. An initial, 1st, 2nd, and 4th hours blood gas results of the patient				
	0 hour	1st hour	2nd hour	4th hour
pH	7.025	7.012	6.921	6.881
pCO_2 (mmHg)	40.3	36.6	22.6	10.5
HCO_3 (mmol/L)	9.1	8.8	6.8	4.8
Lactate (mmol/L)	20.32	22.3	25.02	29.01
Anion gap (mmol/L)	18	20	23	24
Glucose level (mg/dL)	492	410	364	301

and coagulation findings. However, her arterial blood gas analysis on admission was significant for pH: 7.025, pCO_2: 40.3 mmHg, HCO_3: 9.1 mmol/L, lactate: 20.32 mmol/L, anion gap of 18 mmol/L, and glucose level: 492 mg/dL. The patient was observed to develop metformin-induced LA with a high anion gap. After administering 1.5 meq/kg intravenous bolus sodium bicarbonate ($NaHCO_3$), 1.5 meq/kg $NaHCO_3$ infusion was added to the treatment chart. Hemodialysis (HD) therapy was planned due to the progress of metabolic acidosis in the serial blood gas follow-ups (Table 1), and she was taken to the intensive care unit. The patient developed ventricular fibrillation and then cardiac arrest during HD. Despite the administration of defibrillation and cardiopulmonary resuscitation, a normal heartbeat could not be restored, and the patient died in the 4th hour of her patient to the emergency department.

Discussion

Metformin-associated LA (MALA) has been categorized in the literature as follows: 1) MILA: Cases where no known additional conditions that could lead to LA are present except for high-dose metformin use. 2) MALA: Cases where additional other conditions that will cause LA with metformin use. 3) Metformin-unrelated LA: Cases in which LA develops due to other conditions rather than metformin accumulation [7]. Our patient used high-dose metformin, and there were no abnormalities in the initial hemogram, biochemistry, and coagulation parameters. As well as there were no additional conditions that would cause LA in the patient. LA with a high anion gap was present in her blood gas findings on admission. Our patient was evaluated as MILA.

Gastrointestinal decontamination with activated charcoal, hydration, and intravenous $NAHCO_3$ is suggested in MILA. For patients with severe metabolic acidosis, HD is the preferred approach [8]. As well as there are no antidotes for metformin intoxication [9]. Our patient was admitted to the emergency department 4 h after taking the drug. Activated charcoal and gastric lavage was applied to the patient despite the late admission. Additionally, hydration and symptomatic treatment was initiated. HD was rapidly planned for the patient who was started on $NaHCO_3$ therapy because of severe metabolic acidosis during the follow-up. Biguanide group drugs are not antihyperglycemic agents, so hypoglycemia is not expected in single-use [2]. Similarly, hypoglycemia was not observed in our patient follow-up. Therefore, additional dextrose treatment was not necessary.

Metformin increases the conversion of glucose to lactate in the small intestine [10]. Additionally, it inhibits mitochondrial respiratory chain complex 1, leading to decreased hepatic gluconeogenesis from lactate, pyruvate, and alanine [6]. In this way, metformin increases the blood lactate level, but LA rarely occurs unless acute overdose taking. However, mortality is extremely high in patients with LA [11]. Mortality rates in multiple case series range from 26% to 48.3% [5,6,12,13]. In a systematic review, Dell'Aglio et al. [14] evaluated 22 metformin overdose cases and found a correlation between low pH and high lactate level and mortality [14]. In this study, the patient's pH was 7.025, and lactate level was 20.32 mmol/L on admission. High lactate levels and progressive metabolic acidosis were observed in the patient follow-ups. Similar to the literature, our patient developed a devastating condition, and despite early supportive therapy, she was mortal at the 4th hour of her admission to the emergency department.

Conclusion

In conclusion, LA is the cause of metabolic acidosis with an increased anion gap; it can develop rapidly in acute and high-dose metformin intoxication. HD should not be delayed, particularly in cases with MILA. Physicians should remember that these patients are mortal despite aggressive treatment.

Ethics

Informed Consent: Written informed consent obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., T.A., Concept: A.A., T.A., Design: A.A., T.A., Data Collection or Processing: A.A., T.A., Analysis or Interpretation: A.A., T.A., Literature Search: A.A., T.A., Writing: A.A., T.A.

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CASE REPORT

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A Mortal Case of Meningeal Tuberculoma with Isoniazid-induced Encephalopathy

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Abstract

Tuberculosis continues to be a major cause of morbidity and mortality in low-income and middle income countries. The treatment of this disease also has different types of side effects. In this case report we discussed an uniqe and unknown cause of encephalopathy during treatment that induced by the use of isoniazid. There have reported cases of encephalopathy during drug treatment, while the reported case of isoniazid use is almost non-existent. The result of this condition can be as mortal as in this study. Because of that knowing its surgical and medical indications can have benefits to the survey. In this case report, our main aim is to describe these. During the management of cerebral tuberculoma patients, drug induced encephalopathy should be considered a mortal cause. When encephalopathy occurs during tuberculosis treatment, it should be kept in mind that this may occur secondary to isoniazid.

Keywords: Tuberculosis, isoniazid, mortality, tuberculoma

Introduction

Tuberculosis is a multi-systemic infectious disease caused by species of mycobacteria. Tuberculosis affects the central nervous system (CNS) in three different ways: tuberculous meningitis, meningeal tuberculoma and spinal tuberculous arachnoiditis. All three forms are common where tuberculosis incidence is high [1-3]. Among the CNS tuberculosis, the most urgent one is meningitis, while the most rare form is cerebral tuberculoma. Tuberculomas usually present with focal neurological findings. Therefore, it deserves new diagnostic methods, as in other pathologies [4,5]. They may be confused with malignant lesions, sarcoidosis, pyogenic abscesses, toxoplasmosis and cysticercosis [6].

The use of anti-tuberculosis drugs for treating this disease is the standard treatment. The response is generally good following anti-tuberculosis treatment and the prognosis is good after long-term treatment. In the treatment, isoniazid rifampicin is usually used for 4 months after 2 months of treatment with isoniazid pyrazinamide ethambutol rifampicin. Generally, no mortality is observed for treating cerebral tuberculoma [7]. Of the anti-tuberculosis drugs used for treating cerebral tuberculoma, only isoniazid-induced encephalopathy and cerebral edema have been noted [8]. Rifampicin ethambutol and pyrazinamide-induced cerebral edema or encepencephalopathy have not been reported in the literature. In this article, isoniazid-induced encephalopathy that developed during the treatment of cerebral tuberculoma and causes mortality, is discussed.

Case Report

A 55-year-old male patient was brought to the emergency department by his relatives with the complaint of strange behavior. He had no chronic disease. The other neurological and systemic examinations of the patient with impaired orientation to place and time on the admission examination were normal. Initial laboratory values were white blood cell: 12.200; hemoglobin: 14.3. Serum creatinine, blood urea nitrogen, sodium, potassium, glucose, calcium, aspartate transaminase and alanine transaminase were normal. C-reactive protein was 3.72, which was increased (normal range: 0-0.08). Erythrocyte

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sedimentation rate was 28 mm/h and procalcitonin levels were in normal ranges. Multiple diffuse dense lesions were present in the bilateral cerebellum on the cranial computed tomography (CT). The IV contrast-enhanced cranial magnetic resonance imaging (MRI) of the patient showed multiple lesions with hypointense center and hyperintense periphery and no peripheral edema in the T2A sequence and with peripheral contrast uptake in the form of a ring after the administration of IV contrast agent (Figures 1, 2). The findings were evaluated in favor of multiple tubercular the patient was hospitalized in the infectious diseases service. A lumbar puncture of the patient revealed no evidence of meningitis. Patient's glucose was 97/185 and cerebrospinal fluid protein was 8.6. Toxoplasma immunoglobulin G and immunoglobulin M were negative. Venereal disease research laboratory test was negative. Anti-C was negative. No acid-resistant bacteria were seen in the acid resistant bacillus and no cavitary lesion was noted on the thorax CT. The patient with anergic purified protein derivative and positive T-spot test was initiated.

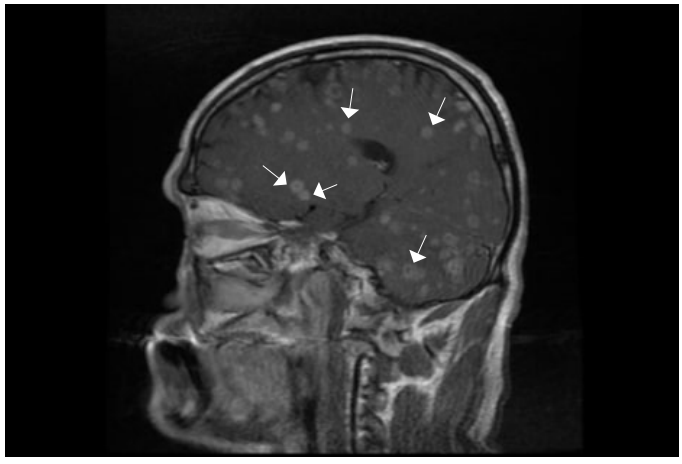

Figure 1. Intravenous contrast-enhanced cranial magnetic resonance imaging of the patient showed sagittal plane (white arrows)

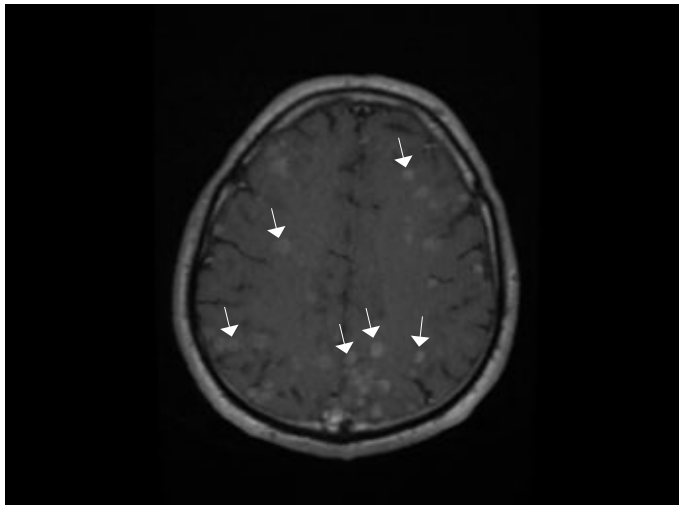

Figure 2. Intravenous contrast-enhanced cranial magnetic resonance imaging of the patient showed transverse plane (white arrows)

Treatment with isoniazid 300 mg, RIF 600 mg, ETM 1000 mg, PRZ 1500 mg and dexamethasone 3*8 mg was started. patient was scheduled for CT-guided biopsy. Biopsy could not be performed since the lesions visualized on MRI could not be distinguished clearly on CT. His neck ultrasonography showed a few reactive lymph nodes located in the left supraclavicular region, the largest of which was 4 mm in diameter. The patient had a severe headache and vomiting on the tenth day of admission. The cranial CT performed on the 10th day of the treatment revealed hydrocephalus. The patient underwent external ventricular drainage surgery. Somnolence and headache complaints persisted after the surgical intervention. On the 16th day of follow-up, the patient died from respiratory distress.

Discussion

Although tuberculosis is a common disease in developing countries, it is an infectious disease caused by mycobacterium tuberculosis, which continues to threaten public health in developed countries due to HIV epidemic and migration [2]. In 1993, the world health organization declared tuberculosis as a global emergency [9]. It is estimated that more than 1.7 billion people worldwide are affected by *tubercle bacillus* [10]. Although the incidence of tuberculosis tends to decline with strict policies implemented, it has not yet reached the desired level. Factors such as low socioeconomic status and access to quality healthcare are important challenges in tuberculosis control [11]. Additionally, drug resistance complicates the treatment [11].

In about 5%-10% of tuberculosis cases, CNS involvement is seen and it may show up as meningitis, solitary tuberculoma, abscess, infarction, or military parenchymal disease. Tuberculomas that may cause neurological findings due to local compression are less common [12].

It has also been reported that clinical tuberculomas may present with symptomatic intracranial mass lesions in regions with a high prevalence of tuberculosis. The usual patients are children or young adults who present with headache, seizure, focal neurological deficits, increased intracranial pressure symptoms [7]. Systemic disease symptoms and meningeal inflammation findings are usually absent [7]. It is usually diagnosed by clinical epidemiological and radiographic data or by needle biopsy. The surgical indications other than diagnosing these lesions are the critical location of the lesion, obstructive hydrocephalus, and brain stem compression [7]. In this study, hydrocephalus was observed on tomography performed on the 10th day.

Tuberculomas usually respond well to anti-tuberculosis treatment. Generally, meningeal tuberculoma cases have a good survival. In our case, the patient developed mortality

on the 16th day after the initiation of anti-tuberculosis treatment. Mortality in this case could not be attributed to a mass effect associated tuberculous tuberculomas. There are also no additional comorbidities that may cause mortality in the patient. Of the anti-tuberculosis drugs used for treating cerebral tuberculoma, only isoniazid-induced encephalopathy and cerebral edema have been noted in previous studies. Rifampicin ethambutol and pyrazinamide-induced cerebral edema or encepencephalopathy have not been reported in the literature. Cerebral edema and encephalopathy developed in the patient was associated with isoniazid. Isoniazid-induced encephalopathy and cerebral edema have been reported by a small number of studies.

Conclusion

It should be known that patient management with isoniazid may cause an isonizaid-induced encephalopathy and mortality in cerebral tuberculoma treatments.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K., Concept: G.A., M.K., Design: G.A., Data Collection or Processing: M.K., G.A., Analysis or Interpretation: M.K., G.A., Literature Search: M.K., G.A., Writing: M.K., G.A.

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