E-ISSN
e-ISSN 2667-8721
**Volume: 3 Issue: 3 December 2021**

www.ejcritical.com

# EURASIAN JOURNAL of CRITICAL CARE

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Emergency Physicians Association of Turkey

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# Editorial

Sağlık gündeminin ülkeyi en çok meşgul ettiği bir zaman diliminde tıbbın doruk noktalarından biri olan kritik bakımla ilgili çalışmalarımızı yayınladığımız dergimizde yılın son sayısında birlikteyiz. Her geçen gün daha çok tanınan gelişen ilginize mazhar olan dergimizin bu sayısında önemli araştırma makaleleri, olgu sunumları ve editöre mektup yer almaktadır. Ülkemizde kritik bakım konusuna verilen önem artmalı bu konuda farklı yapılanmalara gidilmeli başta yöneticiler ve sağlık çalışanları olmak üzere her kesim bu çalışmalara gereken ilgili göstermelidir. Acil tıp hastalarının önemli bir kısmı kritik hasta grubuna girmektedir. Ayrıca tüm branşların kritik hasta grupları vardır. Bu yüzden kritik hasta bakımı çok geniş bir yelpazeyi oluşturmaktadır. Bunun için ayrı bir eğitim gerekmektedir. Başta ABD'de olmak üzere birçok ülkede kritik bakım acil tıbbın bir yan adlı olmaya başlamıştır. Bu çalışmamızın geleceğin yapılanmasına ışık tutmasını diliyor saygılarımı sunuyorum.

Başarı dileklerimle
Prof. Dr. Başar Cander, Baş Editör

We are together in the last issue of the year in our journal, where we publish our studies on critical care, which is one of the pinnacles of medicine, at a time when the health agenda is the most busy in the country. Important research articles, case reports and letters to the editor are included in this issue of our journal, which is getting more and more popular with each passing day. The importance given to critical care in our country should increase, different structures should be made in this regard, and every sector, especially managers and health workers, should show the necessary interest in these studies. A significant portion of emergency medicine patients fall into the critically ill group. In addition, all branches have critical patient groups. Therefore, critical patient care covers a very wide spectrum. A separate training is required for this. In many countries, especially in the USA, critical care has become a sub-branch of emergency medicine. I wish that this work will shed light on the structuring of the future, I present my respects.

Best wishes
Prof. Dr. Başar Cander, Chief Editor

# Contents

Letter
Eurasian Journal of Critical Care

# Acute Phase Response

Abuzer Özkan[1], Serdar Özdemir[1]

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Dear editor,

We have read the article titled "The Role of C-RP / Albumin Ratio in The Diagnosis of Stroke and an Overview of the Factors Affecting Hemispheres" prepared by Tataroğlu and Güven with great interest[1]. We thank the authors and the editorial board for their courage in publishing this negative article that is informative and successful manuscript. As mentioned in an article published in nature, highlighting negative results will improve science[2]. We also would like to mention a few important points about systemic effects of inflammation and acute phase reactants.

Even if the inflammation is local, it can cause cytokine-induced systemic reactions called acute phase response. Systemic effects of acute inflammation in infections and ischemic events have been experienced and reported[1,3]. These systemic effects are mediated by the cytokines that were stimulated bacterial products such as lipopolysaccharides, viral double-stranded RNA and degradation products[4]. Interleukin-1, interleukin-6 and tumor necrosis factor-1 are important mediators of the acute phase reaction4. In particular, type 1 interferons make important contributions to these reactions[4].

Acute phase proteins are mostly synthesized in the liver and are plasma proteins that can increase hundreds of times the plasma concentration in response to inflammatory stimulus3. The most well-known of these proteins are C-reactive protein (CRP), fibrinogen and serum amyloid a protein (SAA)[5]. These proteins are synthesized from the liver as a result of cytokine stimulation[5]. SAA and CRP can bind to the microbial cell wall. They act as opsonin to fix complement[5]. Fibrinogen binds to erythrocytes. This causes the erythrocytes to form clumps and collapse rapidly. This realization forms the pathogenesis of erythrocyte sedimentation rate measurement. While the effects of acute phase proteins are positive in acute inflammation, they may cause secondary amyloidosis in chronic inflammation as in SAA[6].

On the other hand, there are also plasma proteins, most of which are synthesized from the liver and whose plasma concentrations are decreased by inflammation and cytokine stimulation[7]. these proteins are negative acute phase reactants and the most well-known of the group are albumin and transfrerin[7]. Especially albumin is used as a marker of catabolism[7].

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Original Article
Eurasian Journal of Critical Care

# Relationship Between Vitamin D Level As An Independent Risk Factor and One-Year Mortality in Patients With Hospital-Acquired Pneumonia Followed Up in Intensive Care Unit

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## Abstract

**Background:** Hospital-acquired pneumonia (HAP) is an important cause of mortality and morbidity among hospital-acquired infections. Vitamin D (25[OH] D) plays a role as an anti-inflammatory, immunomodulatory, and antimicrobial agent in infections. There are limited studies on the long-term mortality prediction of 25(OH)D deficiency in HAP and the findings are controversial. In this study, our primary aim was to investigate the role of 25(OH)D level measured during hospital admission as an independent risk factor for one-year mortality in HAP patients requiring intensive care.

**Materials and Methods:** The retrospective study included patients that were diagnosed with HAP and admitted to the intensive care unit (ICU) between 2014 and 2018. Relationship between pretreatment 25(OH)D level and one-year independent mortality was evaluated. Vitamin D deficiency was defined as a 25(OH)D level of <30 ng/ml. Patients were divided into two groups based on vitamin D level: (i) <20 ng/ml and (ii) >20 ng/ml.

**Results:** The study included 57 patients comprising 36 (63.2%) men and 21 (36.8%) women with a mean age of 75 years. One-year independent mortality occurred in 21 (36.8%) patients. Mean length of ICU stay was 16 days. Mean 25(OH)D level was 9.53 ng/ml, which was <20 ng/ml in 47 (82.5%) and >20 ng/ml in 10 (17.5%) patients. No significant relationship was found between 25(OH)D level and one-year independent mortality and the length of ICU stay (p=0.477 and p=0.941, respectively). Similarly, no significant relationship was found between 25(OH)D level and APACHE II, age, length of ICU stay, and one-year independent mortality (p=0.621, p=0.933, p=0.410, and p=0.933, respectively).

**Conclusion**: The study included 57 patients comprising 36 (63.2%) men and 21 (36.8%) women with a mean age of 75 years. One-year independent mortality occurred in 21 (36.8%) patients. Mean length of ICU stay was 16 days. Mean 25(OH)D level was 9.53 ng/ml, which was <20 ng/ml in 47 (82.5%) and >20 ng/ml in 10 (17.5%) patients. No significant relationship was found between 25(OH)D level and one-year independent mortality and the length of ICU stay (p=0.477 and p=0.941, respectively). Similarly, no significant relationship was found between 25(OH)D level and APACHE II, age, length of ICU stay, and one-year independent mortality (p=0.621, p=0.933, p=0.410, and p=0.933, respectively).

**Key words:** Hospital-acquired pneumonia, mortality, 25(OH)D, intensive care

## Introduction

Vitamin D plays a role as a biomarker for cell proliferation and differentiation, hormone secretion, immune function regulation, and innate and acquired immune system. Vitamin D has also been shown to have inhibitory properties in T and B lymphocyte differentiation and in the acquired immune system. It transforms into 25 hydroxyvitamin D (25 OH D) in the skin, liver, and kidney and can be used to determine its pool and level since its half-life is two to three weeks.[1-3] Although there is no consensus in the literature regarding its optimal level, vitamin D deficiency is defined as a serum level of <20 ng/ml and vitamin D insufficiency is defined as level of 20-30 ng/ml. In recent studies, vitamin D deficiency has been shown to play a role in mortality associated with diabetes, hypertension, and inflammation-based diseases.[4]

Hospital-acquired pneumonia (HAP) is a pneumonia that develops 48 hours after hospital admission or discharge. HAP ranks second among all hospital-acquired infections worldwide. Moreover, it is an important cause of mortality and morbidity in patients followed up in intensive care unit (ICU).[5-7] Studies investigating community-acquired pneumonia (CAP) have shown that vitamin D plays has important anti-inflammatory, immunomodulatory, and antimicrobial properties. Additionally, it has been suggested that vitamin D deficiency in pneumonia patients is mostly caused by the deterioration of the oxidant/antioxidant balance. Therefore, it is important to detect and replace vitamin D levels during hospital admission. On the other hand, studies conducted on vitamin D level have shown that the risk of lower respiratory tract infection increases at 25(OH)D levels of 30-38 ng/ml.[1,8,9] In a study conducted on critically ill patients followed in ICU, vitamin D deficiency was found to be an independent risk factor for 30- and 90-day and 1-year mortality.[10,11] There is a limited number of studies on the relationship between vitamin D deficiency and long-term mortality in HAP and also there is no consensus regarding this relationship.[12] In the present study, our primary aim was to investigate the

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role of 25(OH)D level measured during hospital admission as an independent risk factor for one-year mortality in HAP patients requiring ICU care.

## Materials and Methods

The retrospective study included patients who were diagnosed with HAP and admitted to ICU between 2014 and 2018. After obtaining an ethics committee approval (Date: June 18, 2020; No: 678), ICU observation charts, patient histories, and chest X-ray images were reviewed for each patient. Inclusion criteria were as follows: a diagnosis of HAP, admission to ICU according to the guidelines of the Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS), and one-year follow-up for independent mortality.[5-7] Additionally, patients whose HAP treatment was initiated after ICU admission, whose vitamin D levels were measured within the first hour of ICU admission, and those who were detected with vitamin D deficiency and received vitamin D replacement were included in the study.[4] Exclusion criteria were as follows: pregnancy, age below 18 years, prior vitamin D, calcium, and thyroid hormone replacement, a history of total thyroidectomy and parathyroidectomy, active malignancy, active infection other than HAP, and connective tissue disease (Table 1). Vitamin D level was studied with the immunoassay method using a Siemens ADVIA Centaur XPT Immunoassay System. Vitamin D deficiency was defined as a 25(OH)D level of <30 ng/ml. Patients were divided into two groups based on vitamin D level: (i) <20 ng/ml and (ii) >20 ng/ml.

**Table 1:** Flowchart of the study

| |
|---|
| Patients admitted to ICU during the study period (n=110) |
| Patients excluded due to exclusion criteria (n=3) |
| Patients with incomplete medical records (n=41) |
| Patients included in the study (n=57) |

## Statistical Analysis

Data were analyzed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptives were expressed as frequencies (n), percentages (%), median, and minimum-maximum values. Normal distribution of variables was assessed using Shapiro-Wilk test. Both dependent and independent variables with nonnormal distribution were compared using Chi-square test and Wilcoxon's signed-rank test. Continuous variables were compared using Student's t-test and Mann-Whitney U test. A p value of <0.05 was considered significant.

## Results

The study included 57 patients comprising 36 (63.2%) men and 21 (36.8%) women with a mean age of 75 years. One-year independent mortality occurred in 21 (36.8%) patients. Mean 25(OH)D level was 9.53 ng/ml. Mean Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were 26 and 5, respectively. Table 2 presents demographic and clinical characteristics of the patients.

**Table 2:** Demographic and clinical characteristics

| **Variables** | **All patients (N=57)** | **Mortality** | | |
|---|---|---|---|---|
| | **Median(Min-Max)** | **No (N=36)**<br>**Median (Min-Max)** | **Yes (N=21)**<br>**Median (Min-Max)** | ***P*** |
| Age (years) | 75 [20-92] | 76.5 [20-92] | 70 [48-90] | **0.011** |
| 25(OH)D | 9.53 [3.20-48.40] | 10.20 [3.20-48.40] | 8.54 [5.36-48.05] | 0.477 |
| SOFA | 5 [2-18] | 4 [2-12] | 8 [3-18] | <0.001 |
| APACHE II | 26 [15-54] | 26.5[15-42] | 25 [16-54] | 0.974 |
| Variables | **All patients (N=57)**<br>**N (%)** | **No (N=36)**<br>**N (%)** | **Yes (N=21)**<br>**N (%)** | ***p*** |
| Gender (male/female) | 36 (63.2) / 21 (36.8) | 23 (63.8) / 13 (36.2) | 13 (61.9) / 8 (38.1) | 0.882 |
| Comorbidity | 51 (89.5) | 34 (94.4) | 17 (81.0) | 0.113 |
| CAD | 20 (35.1) | 14 (38.9) | 6 (28.6) | 0.435 |
| HT | 24 (42.1) | 18 (50.0) | 6 (28.6) | 0.117 |
| DM | 10 (17.5) | 6 (16.7) | 4 (19.0) | 0.821 |
| COPD | 44 (77.2) | 31 (86.1) | 13 (61.9) | **0.037** |
| CKF | 12 (21.1) | 8 (22.2) | 4 (19.0) | 0.779 |
| CHD | 2 (40.4) | 21 (58.3) | 2 (9.5) | **<0.001** |
| Neurological disease | 17 (29.8) | 12 (33.3) | 5 (23.8) | 0.452 |
| ICU stay (days) | 16 [1-96] | 17 [3-96] | 15 [1-48] | 0.941 |

APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CAD: Coronary artery disease, CHD: Coronary heart disease, HT: Hypertension, CKD: Chronic kidney disease, 25(OH)D: 25 25 hydroxyvitamin D, ICU: Intensive care unit

Table 3 presents the microbiological and radiological characteristics assessed at ICU admission. The type of microbiological culture samples established no significant relationship with radiological findings and one-year independent mortality (p=0.064 and p=0.355, respectively).

As an independent risk factor for one-year mortality, 25(OH)D level was found to be low (<30 ng/ml) in 18 (34.6%) and normal (>30 ng/ml) in 3% (60.0%) patients that died during the study.

Table 3 shows the relationship between 25(OH)D levels and demographic and clinical characteristics. No significant relationship was found between 25(OH)D level and one-year independent mortality and the length of ICU stay (p=0.477 and p=0.941, respectively). On the other hand, 25(OH)D level was found to be <20 ng/ml in 47 (82.5%) and >20 ng/ml in 10 (17.5%) patients. No significant relationship was found between 25(OH)D level and APACHE II, age, length of ICU stay, and one-year independent mortality (p=0.621, p=0.933, p=0.410, and p=0.933, respectively) (Table 4).

## Discussion

The results indicated no significant relationship between vitamin D supplementation and one-year independent mortality and the length of ICU stay in HAP patients requiring ICU care.

Vitamin D is a steroid hormone that is vital for lung and bone health.[13] In infections, it decreases the production of inflammatory proteins with no elevation in viral replication in tracheobronchial cells.[14] Studies have shown that vitamin D receptors are available in various immune cells such as neutrophils, macrophages, and dendritic cells. It has also been shown that the secretion of proinflammatory cells such as interleukin-1 (IL-1), IL-6, IL-8, and IL-12, which occur with vitamin D replacement in the presence of inflammation, decreases in individuals with vitamin D deficiency. Based on this hypothesis, it is believed that vitamin D has immunoregulatory and immunomodulatory properties.[15] In recent years, there have been numerous studies conducted on the effect of vitamin D deficiency on the course of the disease, particularly in CAP, while studie evaluating HAP are relatively fewer. A study by Grant et al. [16] found that vitamin D replacement produced antimicrobial peptides and decreased the prevalence of pneumonia caused by influenza virus infection by reducing the production of proinflammatory cytokines. A randomized double-blind placebo-controlled study evaluated 46 ventilator-associated patients and reported that procalcitonin levels decreased significantly after vitamin D replacement in patients with vitamin D deficiency.[15] A prospective observational cohort study by Kempker et al.[17] evaluated vitamin D levels of 314 patients followed up in ICU and suggested that vitamin D deficiency predisposed patients to develop HAP. In our study, we evaluated 25(OH)

**Table 3:** Microbiological and radiological characteristics

| Variables | | N | % |
|---|---|---|---|
| Microbiological sample type | Sputum | 23 | 52.6 |
| | Endotracheal aspirate | 30 | 40.4 |
| | Blood | 4 | 7.0 |
| | Total | 57 | 100 |
| Microbiological culture growth | Pseudomonas Aerugionosa | 13 | 22.8 |
| | Acinetobacter Baumannii | 34 | 59.6 |
| | Acinetobacter Baumannii + Klebsiella Pneumoniae | 9 | 15.8 |
| | Acinetobacter Baumannii + Pseudomonas Aeruginosa | 1 | 1 |
| | Total | 57 | 100 |
| Chest X-ray infiltration | Consolidation | 19 | 33.3 |
| | Consolidation + ground glass opacity | 24 | 42.1 |
| | Ground glass opacity | 6 | 10.5 |
| | Consolidation + parapneumonic effusion | 8 | 14.0 |
| | Total | 57 | 100 |

**Table 4:** Relationship between 25(OH)D levels and demographic and clinical characteristics

| **Variables** | **All patients (N=57) Median (Min-Max)** | **Group 1 (N=47) Median (Min-Max)** | **Group 2 (N=10) Median (Min-Max)** | *p* |
|---|---|---|---|---|
| Age (years) | 75 [20-92] | 78 [61-82] | 74 [20-92] | 0.933 |
| APACHE II | 26 [15-54] | 25 [20-39] | 27 [15-54] | 0.621 |
| ICU stay (days) | 18. 5 [4-96] | 19 [4-96] | 15.5 [5-33] | 0.410 |
| Variables | **All patients (N=57) N (%)** | **Group 1 (N=47) N (%)** | **Group 2 (N=10) N (%)** | ***p*** |
| One-year mortality | 2136.8) | 17(36.2) | 4 | 0.933 |

ICU: Intensive care unit, Group 1: Vitamin D level <20 ng/ml, Group 2: Vitamin D level >20 ng/ml, APACHE II: Acute Physiology and Chronic Health Evaluation II

D levels in HAP patients with a high APACHE II score whose treatment was initiated in ICU. A control group could not be taken due to the retrospective nature of the study. Most of the studies in the literature have evaluated nonspecific hospital-acquired infections in medical ICUs and our study is one of the limited number of studies conducted in HAP patients.

In recent years, studies conducted on different diseases in the general population, different vitamin D deficiency rates have been reported with regard to the variation in ethnic origins, underlying diseases, genders, and seasonal characteristics.[14,18,19] In our study, the rate of additional diseases was 89.5% and additional diseases that may affect vitamin D level could not be standardized due to the retrospective nature of our study. The reference range to be used in the definition of vitamin D deficiency in the evaluation of immunological function remains unclear due to the lack of randomized controlled studies on the optimal dose for the treatment of deficiency.[12] Moreover, the optimal dose to be used in replacement, particularly the one that predisposes patients to bacterial and viral infections, has not been defined.[13] A study evaluated 4257 hospitalized adult patients and reported that the vitamin D level was below 50 nmol/L in 50% of the patients.[20] A retrospective study evaluated critically elderly patients followed up in ICU and found vitamin D deficiency in all (100%) patients.[19] Literature indicates that the cutoff value to be used in the definition of vitamin D deficiency and in the recommended optimal level to be achieved with replacement therapy remain uncertain.[21] In the majority of studies conducted in recent years, vitamin D deficiency has been defined as a 25(OH)D level of <30 ng/ml.[22] The present study evaluated ICU patients with a high APACHE II score and variable intra- and extra-vascular fluid volume due to sepsis. A previous study evaluated patients with sepsis followed up in ICU and reported that the fluid volume changed the level of vitamin D-binding protein by 6-13%.[21] Accordingly, the 25(OH)D levels in our study could be considered lower or higher than those reported in the literature since the hemodynamic status of the patients and the treatments administered could not be standardized and the study had a retrospective nature. Despite all these factors, the 25(OH)D deficiency rate in our patients was 91.2%, which was consistent with the rates reported by the studies conducted with ICU patients.[2,12] However, no statistical cut off value could be determined for 25(OH)D level since the sample size was relatively smaller and no control group of patients followed up in chest diseases clinic was included in the study. On the other hand, in line with the literature, vitamin D level was categorized as <20 ng/ml and >20 ng/ml.[4]

The relationship between 25(OH)D deficiency as a long-term independent risk factor and mortality remains unclear.[12] Graedel et al.[20] evaluated different disease groups and found prolonged hospitalization and increased 30-day in-hospital mortality in patients with 25(OH)D deficiency. In another study conducted in ICU patients, vitamin D deficiency was found to be an independent risk factor for 30- and 90-day and 1-year mortality.[10,11] Mrioliaee et al.[15] evaluated the effect of vitamin D supplementation in patients with ventilator-associated pneumonia and found that the decreased mortality rate achieved with replacement therapy in patients with vitamin D deficiency was independent of the type of microorganism. A study by Amrein et al.[23] evaluated critically ill patients followed up in ICU and found that the length of hospital stay and the rates of in-hospital and six-month mortality did not decrease after the replacement therapy in patients with vitamin D deficiency. Similarly, in our study, no significant relationship was found between 25(OH) D deficiency and one-year independent mortality and the length of ICU stay. To our knowledge, there are few studies in the literature specifically evaluating the relationship between pretreatment 25(OH)D deficiency and long-term independent mortality in HAP patients requiring ICU care, and their findings are controversial.[10,12,23] Nonetheless, our study had several limitations. First, it was not an observational study and was conducted retrospectively with a small number of patients. Second, vitamin D levels were not evaluated according to vitamin D-binding protein levels, which are likely to be affected by ICU care. Third, in patients who received replacement therapy due to vitamin D deficiency, the replacement therapy was not followed up after ICU discharge. Finally, vitamin D level was assessed with a single measurement.

## Conclusion

We consider that multicenter, double-blind randomized controlled studies are needed to substantiate the definition of vitamin D deficiency and the optimal vitamin D level to be achieved with replacement therapy in order to evaluate the effect of the therapy on the course of the disease and long-term independent mortality in HAP patients followed up in ICU.

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Original Article
Eurasian Journal of Critical Care

# Analysis of Patients with Pulmonary Thromboembolism Who Received Thrombolytic Therapy in The Emergency Department

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## Abstract

**Introduction:** Pulmonary embolism (PE) is a life-threatening but potentially reversible emergency condition that occurs as a result of the obstruction of pulmonary arteries. We aimed to assess the demographic features, laboratory data, and mortality rates of patients with pulmonary embolism who were administered thrombolytic therapy in this study.

**Material and Methods:** This was a retrospective study. It enrolled patients who received thrombolytic therapy for PE at the Emergency Medicine. The demographic data, comorbidities, physical examination findings and laboratory parameters of the patients with PE were retrospectively recorded.

**Results:** Sixteen patients were enrolled during the study. The most common symptoms were dyspnea (68.8%), syncope (62.5%), and chest pain (23.5%). Nine patients were brought to the emergency department with cardiac arrest, and 4 patients died at the emergency department. The 30-day mortality rate was 62.5%. When demographic and laboratory parameters were compared according to 30-day mortality among the patients who died and survived, there was no statistically significant difference in any parameter between the two groups. (p>0.05 for all parameters).

**Conclusion**: Systemic thrombolytic therapy is the first treatment option for patients with PE who are in shock or who have profound hypotension or hemodynamic instability. In this study, we showed that patients admitted to the emergency department with hemodynamic instability or cardiac arrest were abnormal in laboratory parameters, received lower doses of thrombolytic therapy and had higher mortality.

**Key words:** Pulmonary thromboembolism, thrombolytic therapy, emergency

## Introduction

Pulmonary embolism (PE) is a life-threatening but potentially reversible emergency condition that occurs as a result of the obstruction of pulmonary arteries[1]. PE is a common cardiopulmonary disease with an annual incidence of more than 0.1% in the United States of America[1]. The mortality rate of acute PE is between 7% and 11%[2]. It is more common among males in all age groups, and its mortality is higher in male sex and among the elderly[2,3].

The mortality and morbidity rates of PE have been reduced over the past years, particularly by advances in diagnosis, risk assessment, and treatment as well as anticoagulation. Pulmonary embolism has no specific clinical and physical examination findings, but high suspicion is essential for diagnosis. Ventilation/perfusion (V/Q) scintigraphy, computerized tomography angiography (CTA), lower extremity venous Doppler ultrasonography (USG), and echocardiography (ECHO) are the diagnostic tools with increased reliability and effectiveness[2, 3]. Since it is a disease with high mortality and morbidity, anticoagulant therapy is mostly initiated when embolism is suspected. Unless there is an absolute contraindication to thrombolytic therapy, it is the most effective treatment option for moderate-to-high risk PE[3, 4]. However, adverse events with thrombolytic therapy which may result in death are reported in 15-20% of cases[5].

Patients with high-risk PE presenting with shock or hypotension are at high risk of death at the hospital, particularly within a few hours after admission[6]. Therefore, thrombolytics should be given to all patients with high-risk PE unless there is an absolute contraindication[3, 4]. In this study, we aimed to assess the demographic features, laboratory data, and mortality rates of patients with pulmonary embolism who were administered thrombolytic therapy.

## Materials and Method

This was a retrospective study. Ethical approval for this study was obtained from local Hospital Ethics Committee (2012-KAEK-15/2111, 10/06/2020). It enrolled patients who received thrombolytic therapy for PE at the Emergency Medicine Clinic between 01.01.2014 and 01.11.2019. At our clinic, thrombolytic therapy is administered to hemodynamically unstable patients in compliance with the current

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guidelines. Alteplase (Actilyse®) 100 mg is infused for 2 hours or, in patients with cardiac arrest, it is administered as intravenous (IV) bolus at a dose of 50 mg.

The demographic data, comorbidities, previous surgeries, vital signs, physical examination findings, laboratory parameters, and consultations of the patients with PE were retrospectively recorded from the hospital automation system and the medical records. Deaths at the emergency department and by the 30th day were also recorded. The patients with missing medical data and those who were not administered thrombolytic therapy were excluded from the study.

## Statistical Analysis

Study data were analyzed using IBM SPSS 20.0 (Chicago, IL, USA) statistical software. Normality of discrete and continuous variables was tested using Kolmogrov Smirnov test. Descriptive statistics included median and IQR25-75 (interquartile range) for discrete and continuous variables and number and (%) for categorical variables. Categorical variables were compared using Chi-square test and continuous variables using Mann Whitney-U test.

The results were considered statistically significant at a level of $p<0.05$.

## Results

Sixteen patients were enrolled during the study period. Seven (43.8%) patients were women, and the median age of the patients was 65 years (IQR 25-75%: 46.2-84.7 years). The most common comorbidity was hypertension (31.3%). The most common symptoms were dyspnea (68.8%), syncope (62.5%), and chest pain (23.5%). Seventy-five percent of the patients had hypotension that required inotrope infusion. Nine patients were brought to the emergency department with cardiac arrest, and 4 patients died at the emergency department. The 30-day mortality of our 16 patients was 62.5% (n=10). Eight of these patients (80%) were brought to the emergency department with cardiac arrest. The 30-day mortality rate of our patients who were admitted as cardiac arrest was 88.8% (n=8).

The demographic features and some laboratory results of the patients were shown in Table-1.

The laboratory results of the patients were shown in Table 2.

A comparison of age, sex, thrombolytic doses, and laboratory parameters between the deceased and surviving patients at the end of the 30th day revealed that although deceased patients had lower hemoglobin, pH, pCO2, and HCO3, and a higher white blood cell (WBC), pCO2, lac-

**Table 1:** Demographic data of patients

| **Variables** | N=16 |
|---|---|
| **Age, years** median (IQR25-75) | 65 (46.2-84.7) |
| Gender n (%) | |
| Female | 7 (43.8%) |
| Male | 9 (56.3%.) |
| **Co-morbidities** n (%) | |
| Hypertension | 5 (31.3%) |
| Diabetes mellitus | 4 (25%) |
| Chronic obstructive pulmonary disease | 1 (6.3%) |
| Coronary artery disease | 3 (18.8%) |
| Heart failure | 2 (12.5%) |
| Chronic renal disease | 3 (18.8%) |
| **Risk factors for thromboembolism** n (%) | |
| Lower extremity fracture | 4 (25%) |
| Previous surgery | 1 (6,3%) |
| Deep vein thrombosis | 3 (18.8%) |
| Malignancy | 1 (6,3%) |
| **Symptoms** n (%) | |
| Dyspnea | 11 (68.8%) |
| Syncope | 10 (62.5%) |
| Chest pain | 4 (23.5%) |
| Cardiac arrest | 9 (56.3%) |
| **Vital sings** median (IQR25-75) | |
| Systolic blood pressure mmHg | 80 (53.2-98.5) |
| Diastolic blood pressure mmHg | 50 (33.7-61.2) |
| Heart rate /minute | 105 (66-121) |
| Glasgow Coma Scale, median (IQR25-75) | 5.5 (3-15) |
| **Elevation of troponin** n (%) | 9 (56.3%) |
| **Inotrope requirement** n (%) | 12 (75%) |
| **Outcome** n (%) | |
| Mortality in emergency department | 4 (25%) |
| ICU hospitalization | 12 (75%) |
| **Thrombolytic Dose** n (%) | |
| 50mg | 9 (56.3%) |
| 100 mg | 7(43.7%) |
| **Thrombolytic Dose** mg median (IQR 25-75) | 50 (50-100) |
| **Stay of hospital length,** day median (IQR 25-75) | 4 (0-7) |
| **30-day mortality** n (%) | 10 (62.5%) |

**Table 2:** Laboratory findings of all patients

| **Variables, median (IQR25-75)** | |
|---|---|
| Hemoglobin | 13.2 (12.8-14.4) |
| White blood cell | 12.6 (8.8-13.9) |
| Platelet | 205 (126-282) |
| Ph | 7.24 (7.13-7.33) |
| PO2 | 47(28.5-67) |
| PCO2 | 39.3 (31.5-56.4) |
| HCO3 | 19 (13.5-20.6) |
| Lactate | 5.7 (4.1-8.1) |
| Glucose | 149 (130-242) |
| Aspartate Transaminase | 48 (11-84.5) |
| Alanine Amino Transferase | 39.5 (21.7-84) |
| Creatinin | 1.08 (0.93-1.34) |
| Lactate dehydrogenase | 389 (315.5-453.7) |
| Albumin | 3.75 (3-3.9) |

tate, glucose, Alanine Amino Transferase (ALT), Aspartate Transaminase (AST), creatinine, and troponin level, statistical significance was not reached for any parameter ($p>0.05$ for all parameters). The patients who died were administered a lower thrombolytic dose (Table 3).

## Discussion

Pulmonary embolism represents a disease spectrum from an asymptomatic condition to death. Signs and symptoms of PE depend on a patient's cardio-pulmonary reserve and age as well as the location, size, unilateral or bilateral pulmonary vascular involvement, and the recurrence of a thrombus[7, 8]. Dyspnea is the most common symptom[9]. It was also the most common symptom in our patient group. The most remarkable aspect of our study is the high number of patients who had a cardiac arrest. During the study period, 252 patients were diagnosed with PE, 6.3% of whom received thrombolytic therapy. About half of our patients were brought to the emergency department in cardiac arrest status. As our hospital does not contain a chest disease clinic, patients diagnosed with PE are referred to another center for admission to a regular ward or intensive care unit before or after thrombolytic therapy, with the latter to be administered at the referral center whenever possible. We rapidly administer thrombolytic therapy particularly to patients with pre-arrest status or embolism-induced arrest, which, to our opinion, led to a high number of cases admitted with cardiac arrest.

Thrombolytic medications are the pharmacological substances that convert plasminogen to plasmin and actively lyse a thrombus. Early thrombus resolution rapidly fixes increased pulmonary arterial pressure/resistance and accompanying right ventricular dysfunction. Thrombolysis is achieved more rapidly by thrombolytic therapy than heparin, particularly in the first 24 hours [10, 11]. Patients with hemodynamic instability constitute 5-10% of all cases of pulmonary embolism[12, 13]. Seventy-five percent of our cases had hypotension requiring inotrope therapy. Right ventricular dysfunction is found in 30-50% of cases. The presence of both parameters indicates a poor prognosis[13-15]. Thrombolytic therapy reduces mortality by normalizing hemodynamic parameters and right ventricular function. However, its effect on long-term mortality and prognosis is controversial[16]. Besides, an increased risk of major bleeding associated with the use of thrombolytics should also be considered. Thrombolytic agents used for PE are the ones that have been most extensively studied for Acute PE and include recombinant tissue plasminogen activator (tPA), streptokinase, and recombinant human urokinase. Alteplase is used in our clinic. Intravenous alteplase 100 mg is administered via continuous infusion for 2 hours. In more urgent cases (for example, precardiac arrest), it is recommended to administer tPA as a bolus at first and 15th minutes or as a 20 mg IV bolus followed by infusion of 80 mg tPA for 2 hours[6, 17, 18]. However, none of these regimens has been compared with the classical two-hour tPA infusion. Evidence from small randomized studies, on the other hand, suggests that shorter infusions

**Table 3:** Comparison of laboratory and thrombolytic doses according to patients' 30-day mortality

| Variables, median (IQR25-75) | Survived (n=6) | Non survived (n=10) | p value |
|---|---|---|---|
| Age, year | 58 (37-87) | 65 (50.7-82.5) | 0.586 |
| Gender n (%)<br>Male | <br>4 (57.1%) | <br>5 (50%) | <br>0.581 |
| Hemoglobin | 13.8 (13.2-16.4) | 12.9(10.9-14.2) | 0.111 |
| White blood cell | 9.3 (7.4-13.1) | 13.2 (10.3-15.4) | 0.205 |
| Platelet | 183 (123-267.5) | 219 (153-285.5) | 0.640 |
| Ph<br>PO2<br>PCO2<br>HCO3 | 7.28 (6.95-7.36)<br>49 (32.7-69)<br>47.1 (35.1-79.7)<br>19.8 (12.4-20.2) | 7.20 (7.13-7.30)<br>44.7 (24-71)<br>37.8 (25-52.9)<br>17.5 (13.5-21.4) | 0.589<br>0.877<br>0.280<br>0.998 |
| Lactate | 3.8 (2.1-5.9) | 6.5 (4.8-9.6) | 0.064 |
| Glucose | 131 (122-188.5) | 172 (137-345) | 0.125 |
| Aspartate Transaminase | 39 (11.5-98.5) | 61 (13.5-92) | 0.739 |
| Alanine Amino Transferase | 34 (20.5-53) | 42 (25.5-148) | 0.317 |
| Creatinin | 1.06 (1-1.2) | 1.28 (0.86-1.79) | 0.894 |
| Lactate dehydrogenase | 451 (345-572) | 349 (252-397.5) | 0.149 |
| Albumin | 3.6 (3.1-3.9) | 3.7 (2.9-3.95) | 0.941 |
| Elevation of troponin n (%) | 2 (33.3%) | 7 (70%) | 0.302 |
| Thrombolytic Dose | 75 (50-100) | 50 (50-100) | 0.705 |

(i.e. ≤2 hours) more rapidly achieve thrombolysis and are associated with lower bleeding rates compared to longer infusions [6,17]. Kiser et al. reported that half-dose Alteplase, as compared with the full dose, was associated with similar mortality and major bleeding rates although patients who received a half dose more commonly required dose adjustment. According to these results, the authors stressed that questions remained whether half dose Alteplase has similar efficacy as the full dose[19]. It is recommended that thrombolytic therapy be used as bolus infusion in patients presenting with PE-related cardiac arrest[6].

We observed that the majority of our deceased patients were brought to the emergency department with cardiac arrest or were more hemodynamically unstable or had more abnormal laboratory parameters compared to surviving patients. We similarly found that 80% (n=8) of the deceased patients (30-day mortality) presented to the emergency department with cardiac arrest, and thus this patient group received a lower thrombolytic dose than the surviving patients.

It has been shown that moderate-to-severe hypoxemia caused by acute PE leads to hepatopathy, liver function abnormalities, and reduced albumin synthesis[20,21]. It has also been found that these abnormalities were more profound in patients with severe hypoxemia and hemodynamic instability than those with mild hypoxemia. In a study reported by Aslan where liver function tests (LFTs) were investigated among patients with pulmonary embolism, it was found that similar to our results, LFT abnormalities were more common in patients with severe hypoxemia and hemodynamic compromise[20]. Identification of apparently stable patients at high risk of rapid clinical deterioration is critically important for optimizing decisions concerning the intensive care admission from the emergency department, and treatment. For this purpose, various potential prognostic markers like troponin, brain natriuretic peptide (BNP), and echocardiogram have been studied, and troponin and lactate elevations were found to correlate to mortality[22-24]. Lactate is known to predict clinical outcomes in patients with sepsis and trauma. Considering that pulmonary embolism (PE) may lead to lactic acidosis via hypoperfusion or hypoxia, several studies have tested lactate levels for mortality prediction in PE[22,23]. In a prospective study reported from Italy assessing lactate levels for mortality prediction, a lactate level above 2 mmol/L without concomitant shock or hypotension had a positive predictive value of 16% and a negative predictive value of 98% for the prediction of 30-day all-cause mortality[22]. Likewise, a higher lactate level was shown to correlate to shock development, the need for mechanical ventilation, and vasopressor administration[23]. Also, our deceased patients had a saliently higher [6.5 mmol/L (IQR 25-75, 4.8-9.6)] lactate level than the survivors. Our results revealed that most of the deceased patients presented to the emergency department with cardiac arrest were hemodynamically more unstable and had more abnormal laboratory parameters.

## Limitations

Our study has some limitations. First of all, it was a single-center study, with its results being non-generalizable to all centers. Secondly, it was a retrospective study, thus deficient or erroneous data obtained from hospital records may have affected our study results. Also because of the patient diagnoses (ICD codes) were not entered properly, a smaller number of patients may have been included in the study.

Although there was some difference between the laboratory parameters of the deceased and surviving patients, they did not reach statistical significance, which may have stemmed from the small numbers of patients in the study groups, thereby widening the confidence intervals.

## Conclusion

Systemic thrombolytic therapy is the first treatment option for patients with PE who are in shock or who have profound hypotension or hemodynamic instability. Herein, we showed that, among patients presenting to the emergency department with greater hemodynamic instability or cardiac arrest, laboratory parameters were abnormal, which led to the administration of a lower dose of thrombolytic therapy and higher mortality.

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Original Article
Eurasian Journal of Critical Care

# The Files of Patients Who Were Diagnosed with Drug Intoxication, Research Laboratory Analysis

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## Abstract

**Objective:** In this study, we aimed to evaluate the relationship between laboratory electrolyte disturbances and drugs taken in poisoning cases who applied to the Emergency Department and took drugs for suicidal purposes.

**Materials and Methods:** This study is a retrospective study. Patients aged 18 years and older who were diagnosed with drug poisoning in the Adult Emergency Clinic of Okmeydanı Training and Research Hospital Emergency Medicine Clinic were included in the study. Data analysis was done in SPSS 15.0 program. The significance level was taken as $p<0.05$.

**Results:** 162 patients were included in the study. The mean age of the patients was 27 (range 18-61) years. Thirty-four (20.99%) of the patients were male. Considering the frequency of the drugs taken, 34 (21.1%) of the patients had NSAIDs (most common), 33 (20.5%) had paracetamol and/or its compounds, 29 (17.7%) had SSRI, had TCA, 149 (55.3%) had other drugs. It was observed that the serum Na values of the patients who took and did not take high-dose NSAIDs changed statistically ($p=0.000$). The laboratory test results of the patients who took and did not take these drugs were compared, and no statistically significant difference was found ($p>0.05$).

**Conclusion**: According to our suicidal study findings, the amount of drugs taken by our patients is not correlated with their blood levels. Although more than half of our patients have taken toxic doses of the drugs, most of the poisonings are mild and our results can not be generalized to severe poisoning cases.

**Key words:** Electrolyte, paracetamol, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants

## Introduction

Cases of poisoning as a result of drug intake are common medical emergencies. Poisoning; is the event that an organic or inorganic substance adversely affects the functioning of any system in the organism, partially or completely. In case of high intake, every drug or substance has the possibility of turning into poison. Although poisoning usually occurs after oral intake, it can also occur in many ways such as inhalation, insufflation, skin and mucous membranes, or injection.

The first application center of the patients with drug intoxication is usually the emergency department. Nature and amount of the substance taken, time interval between intake of the drug and admission to the hospital, are of great importance in terms of the first intervention and treatment in the hospital.

High-dose drug intake remains the most common cause of poisoning all over the world. Among the substances taken for suicidal purposes, analgesics, antibiotics, antidepressants, antiepileptics, antihistamines are the most common. In the United States (USA), approximately 2-5 million high-dose drug intake patients are observed in a year [1]. Patients may not know that tricyclic antidepressants (TCA), which they take regularly and recommended by their doctors, can be lethal in high doses, or that antihistamines can be less lethal.

Studies examining toxic dose drug exposures and laboratory electrolytes together are rare. In this study, we aim to evaluate the types of laboratory electrolyte disorders and its relationship between the drugs taken in cases of poisoning who applied to the Emergency Service and took drugs for suicidal purposes.

## Methods and Materials

This study is a retrospective study. patients diagnosed with drug intoxication in the Adult Emergency Clinic of Okmeydanı Training and Research Hospital Emergency Medicine Clinic were included in the study. Those with missing data and patients under the age of 18 were excluded from the study.

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After obtaining the approval of the Okmeydanı Training and Research Hospital Senate Ethics Committee with protocol number 281 and dated March 03, 2015, the ethics committee of Okmeydanı Training and Research Hospital, Emergency Medicine Clinic Adult Emergency Service between January 1, 2014, and January 1, 2015, who took suicidal drugs aged 18 years or older. Hospital file records were examined in order to evaluate the cases. Information was obtained about the arrival time, medications, toxic overdose, pregnancy, and hospitalization status of the patients. Hemoglobin, glucose, Na+, K+, Ca, Urea, Cr, AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (T.Bil), International Normalized Ratio (INR) laboratory values of the patients were evaluated. Partial thromboplastin time (aPTT), cardiac enzymes (CE) Troponin T (Trop T), pH, bicarbonate (HCO3) values in AKG were examined. The reference ranges of the laboratory parameters are given in Table 1.

**Table 1:** Reference range of laboratory values

| | Reference Range | Unit |
|---|---|---|
| $Na^+$ | 136-145 | mmol/dL |
| $K^+$ | 3.5-5.1 | mmol/dL |
| BUN | 15-43 | mg/dL |
| Cr | 0.57-1.11 | mg/dL |
| AST | <34 | U/L |
| ALT | <55 | U/L |
| GGT | <36 | U/L |
| T. Bil. | 0.2-1.2 | mg/dL |
| ALP | <150 | U/L |
| Trop-T | <0.014 | ng/mL |
| Calcium | 8.4-10.2 | mg/dl |
| Hb | 11.5-15.5 | g/dL |
| PH | 7.35-7.45 | |
| $HCO_3$ | 22-26 | mmol/L |
| aPTT | 21-37 | sn |
| INR | 0.8-1.2 | INR |

BUN: Blood urea nitrogen, Cr: Creatinine ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: gamma-glutamyl transferase, T.Bil: Total Bilirubin, ALP: Alkaline phosphatase, Hb: hemoglabin, aPTT: activated partial prothrombin time, INR: international normalized ratio,

## Statistical

Statistical analyzes were performed in IBM SPSS for Windows Version 16.0 package program. Numerical variables were summarized as mean ± standard deviation, median [minimum – maximum] values. Categorical variables were shown as numbers and percentages. The difference between the groups in terms of categorical variables was investigated using the chi-square test and Fisher's exact test. The Significance level was taken as $p<0.05$.

## Results

162 patients were included in the study. The mean age of the patients was 27 (range 18-61) years. Thirty-four (20.99%) of the patients were male and 128 (79.01%) were female. Age distrubition of the patients according to their sex is stated in Figure 1.

While 125 (77.1%) of the patients were taking medication above the maximum recommended daily dose, 25 (15.4%) were taking medication at or below the daily recommended dose, drug types and dose amounts were not known in 12 (7.5%) patients.

Considering the frequency of the drugs taken, it was estimated that 34 (21.1%) of the patients had NSAIDs (most common), 33 (20.5%) had paracetamol and/or its compounds, 29 (17.7%) had SSRI, 25 (15.5%) had TCA, 149 (55.3%) had other drugs (Table 2).

When the Na+ values of the patients who took high-dose and non-high-dose NSAIDs were compared, it was found that the Na+ value changed statistically (p=0.000). When the Na+, K+, Urea, Cr, AST, ALT, T.Bil, GGT, ALP, INR, aPTT,

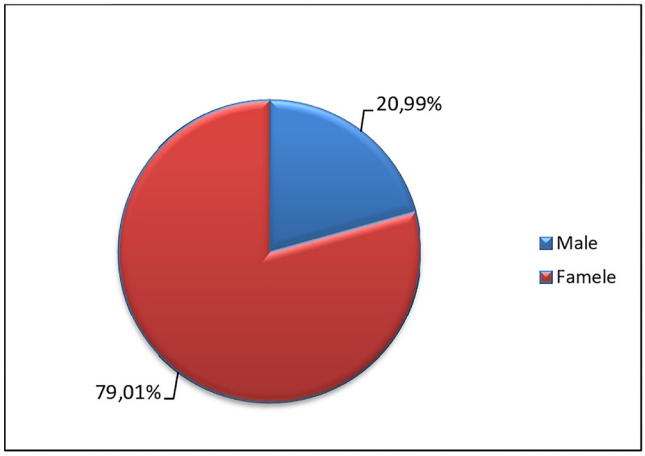


**Figure 1:** Sex percentages of patients

**Table 2:** Frequency of the drugs taken

| | | n | Percentile of the drugs | Percentile of the cases |
|---|---|---|---|---|
| Drugs | Paracetamol | 33 | 12,2% | 20,5% |
| | NSAID | 34 | 12,6% | 21,1% |
| | SSRI | 29 | 10,6% | 17,7% |
| | TCA | 25 | 9,3% | 15,5% |
| | Other | 149 | 55,3% | 99,8% |
| Total | | 270 | 100,0% | 167,7% |

n: number of the patients
NSAID: Non-steroidal anti-inflammatory drugs
SSRI: Selective serotonin reuptake inhibitors
TCA: Tricyclic antidepressant

pH, HCO3 values of the other parameters measured were compared, no statistically significant difference was found (p>0.05). (Table 3)

Na+, K+, Urea, Cr, AST, ALT, T.bil, GGT, ALP , aPTT, INR values of the patients who received high-dose paracetamol and non-high-dose paracetamol were compared, no statistically significant difference was found (p>0.05). In addition, no significant relationship was found in the CEs examined. (Table 4)

Na+, K+, Urea, Cr, AST, ALT, T.Bil, GGT, ALP , aPTT, INR, pH, HCO3 values of the patients receiving high-dose SSRI and non-high-dose SSRI were compared, no statistically significant difference was found (p>0.05). ). In addition, no significant relationship was found in the CEs examined (p>0.05). (Table 5)

**Table 3:** Laboratory values of the patients taking NSAIDs

| Laboratory values seen in patients taking high-dose NSAIDs | | | | | Laboratory values seen in patients taking normal or low-dose NSAIDs | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Low | Normal | High | Total(n) | | Low | Normal | Hig | Total (n) | p |
| $Na^+$ | 3 | 22 | 0 | 25 | $Na^+$ | 0 | 9 | 0 | 9 | 0,000 |
| $K^+$ | 3 | 22 | 0 | 25 | $K^+$ | 0 | 9 | 0 | 9 | 0,383 |
| BUN | 0 | 25 | 0 | 25 | BUN | 0 | 9 | 0 | 9 | - |
| Cr | 0 | 24 | 1 | 25 | Cr | 0 | 9 | 0 | 9 | 1,000 |
| | | | | | | | | | | |
| AST | 0 | 24 | 1 | 25 | AST | 0 | 9 | 0 | 9 | 1,000 |
| ALT | 0 | 24 | 1 | 25 | ALT | 0 | 9 | 0 | 9 | 1,000 |
| GGT | 0 | 24 | 1 | 25 | GGT | 0 | 9 | 0 | 9 | 1,000 |
| T.Bil. | 0 | 24 | 1 | 25 | T.Bil. | 0 | 8 | 1 | 9 | 0,506 |
| ALP | 0 | 0 | 0 | 25 | ALP | 0 | 9 | 0 | 9 | - |
| aPTT | 0 | 25 | 0 | 25 | aPTT | 0 | 0 | 0 | 0 | - |
| INR | 0 | 25 | 0 | 25 | INR | 0 | 0 | 0 | 0 | - |
| PH | 1 | 18 | 1 | 20 | PH | 0 | 7 | 0 | 7 | 0,500 |
| $HCO_3$ | 8 | 12 | 0 | 20 | $HCO_3$ | 0 | 7 | 0 | 7 | 0,780 |

BUN: Blood urea nitrogen, Cr: Creatinine ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: gamma-glutamyl transferase, T.Bil: Total Bilirubin, ALP: Alkaline phosphatase, Hb: hemoglabin, aPTT: activated partial prothrombin time, INR: international normalized ratio

**Table 4:** Laboratory values of the patients taking Paracetamol

| Laboratory values seen in patients taking high-dose paracetamol | | | | | Laboratory values seen in patients taking normal or low-dose paracetamol | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Low | Normal | High | Total (n) | | Low | Normal | High | Total (n) | p |
| $Na^+$ | 3 | 21 | 0 | 24 | $Na^+$ | 0 | 9 | 0 | 9 | 0,326 |
| $K^+$ | 6 | 18 | 0 | 24 | $K^+$ | 1 | 8 | 0 | 9 | 0,156 |
| BUN | 0 | 24 | 0 | 24 | BUN | 0 | 9 | 0 | 9 | - |
| Cr | 0 | 24 | 0 | 24 | Cr | 0 | 9 | 0 | 9 | - |
| | | | | | | | | | | |
| AST | 0 | 24 | 1 | 25 | AST | 0 | 7 | 1 | 8 | 0,558 |
| ALT | 0 | 24 | 1 | 25 | ALT | 0 | 8 | 0 | 8 | 1,000 |
| GGT | 0 | 24 | 1 | 25 | GGT | 0 | 8 | 0 | 8 | 1,000 |
| T.Bil. | 0 | 24 | 1 | 25 | T.Bil. | 0 | 8 | 0 | 8 | 1,000 |
| ALP | 0 | 24 | 1 | 25 | ALP | 0 | 8 | 0 | 8 | - |
| aPTT | 0 | 9 | 0 | 9 | aPTT | 0 | 3 | 0 | 3 | - |
| INR | 0 | 9 | 0 | 9 | INR | 0 | 3 | 0 | 3 | - |
| Trop-T | 0 | 10 | 0 | 10 | Trop-T | 0 | 2 | 0 | 2 | - |

BUN: Blood urea nitrogen, Cr: Creatinine ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: gamma-glutamyl transferase, T.Bil: Total Bilirubin, ALP: Alkaline phosphatase, Hb: hemoglabin, aPTT: activated partial prothrombin time, INR: international normalized ratio

Na+, K, Urea, Cr, AST, ALT, T.Bil, GGT, ALP , aPTT, INR, pH, HCO3 values of patients receiving high-dose TcA and non-high-dose TSA were compared, no statistically significant difference was found (p>0.05). ). In addition, no significant relationship was found in the CEs examined (p>0.05). (Table 6)

## Discussion

We obtained two results in this study, in which we evaluated the laboratory analyzes of the patients who applied to the emergency department for suicidal drug intoxication. First result was that although most of the patients had taken toxic doses of drugs, there was a weak correlation between the amount taken by the patients and their blood drug levels. Second result was that Na levels decreased in the patients taking NSAID. In our point of view, this may indicate that NSAI drugs cause effects at the cellular level.

According to the studies investigated in the literature, average age of high-dose drug poisoning was between 21-31 years[1,2,3]. In this study, the median age was 27 (18-61) years. The median age for women was 27 (18-57), while the median age for men was 29 (18-61). In a study examining 2,229 patients who applied to the emergency department with poi-

**Table 5:** Laboratory values of the patients taking SSRI

| Laboratory values seen in patients taking high-dose SSRI | | | | | Laboratory values seen in patients taking normal or low-dose SSRI | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Low | Normal | High | Total (n) | | Low | Normal | High | Total (n) | p |
| $Na^+$ | 4 | 18 | 0 | 22 | $Na^+$ | 1 | 6 | 0 | 7 | 1,000 |
| $K^+$ | 2 | 20 | 0 | 22 | $K^+$ | 0 | 6 | 1 | 7 | 0,081 |
| BUN | 0 | 22 | 0 | 22 | BUN | 0 | 7 | 0 | 7 | - |
| Cr | 0 | 22 | 0 | 22 | Cr | 0 | 7 | 0 | 7 | - |
| | | | | | | | | | | |
| AST | 0 | 20 | 2 | 22 | AST | 0 | 6 | 1 | 7 | 0,536 |
| ALT | 0 | 21 | 1 | 22 | ALT | 0 | 7 | 0 | 7 | 1,000 |
| GGT | 0 | 20 | 2 | 22 | GGT | 0 | 7 | 0 | 7 | 1,000 |
| T.Bil. | 0 | 22 | 0 | 22 | T.Bil. | 0 | 6 | 1 | 7 | 0,170 |
| ALP | 0 | 22 | 0 | 22 | ALP | 0 | 7 | 0 | 7 | - |
| aPTT | 0 | 11 | 0 | 11 | aPTT | 0 | 0 | 0 | 0 | - |
| INR | 0 | 11 | 0 | 11 | INR | 0 | 0 | 0 | 0 | - |
| PH | 1 | 17 | 0 | 18 | PH | 0 | 2 | 0 | 2 | 1,000 |
| $HCO_3$ | 5 | 12 | 1 | 18 | HCO3 | 0 | 2 | 0 | 2 | 0,219 |

BUN: Blood urea nitrogen, Cr: Creatinine ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: gamma-glutamyl transferase, T.Bil: Total Bilirubin, ALP: Alkaline phosphatase, Hb: hemoglabin, aPTT: activated partial prothrombin time, INR: international normalized ratio

**Table 6:** Laboratory values of the patients taking TCA

| Laboratory values seen in patients taking high-dose TCA | | | | | Laboratory values seen in patients taking normal or low-dose TCA | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Low | Normal | High | Total | | Low | Normal | High | Total | p |
| $Na^+$ | 3 | 17 | 1 | 21 | $Na^+$ | 1 | 5 | 0 | 6 | 0,8660 |
| $K^+$ | 3 | 16 | 1 | 20 | $K^+$ | 0 | 6 | 0 | 6 | 0,3340 |
| BUN | 0 | 21 | 0 | 21 | BUN | 0 | 6 | 0 | 6 | - |
| Cr | 0 | 20 | 1 | 21 | Cr | 0 | 6 | 0 | 6 | 1,0000 |
| | | | | | | | | | | |
| AST | 0 | 20 | 1 | 21 | AST | 0 | 6 | 0 | 6 | 1,0000 |
| ALT | 0 | 20 | 1 | 21 | ALT | 0 | 6 | 0 | 6 | 1,0000 |
| GGT | 0 | 20 | 1 | 21 | GGT | 0 | 6 | 0 | 6 | 1,0000 |
| T.Bil. | 0 | 21 | 0 | 21 | T.Bil. | 0 | 5 | 1 | 6 | 0,1250 |
| ALP | 0 | 21 | 0 | 21 | ALP | 0 | 6 | 0 | 6 | - |
| aPTT | 0 | 12 | 0 | 12 | aPTT | 0 | 1 | 0 | 1 | - |
| INR | 0 | 12 | 0 | 12 | INR | 0 | 1 | 0 | 1 | - |
| Trop-T | 0 | 13 | 0 | 13 | Trop-T | 0 | 2 | 0 | 2 | - |
| PH | 2 | 17 | 0 | 19 | PH | 0 | 3 | 1 | 4 | 0,0930 |
| $HCO_3$ | 5 | 13 | 1 | 19 | $HCO_3$ | 0 | 3 | 1 | 4 | 0,0210 |

BUN: Blood urea nitrogen, Cr: Creatinine ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: gamma-glutamyl transferase, T.Bil: Total Bilirubin, ALP: Alkaline phosphatase, Hb: hemoglabin, aPTT: activated partial prothrombin time, INR: international normalized ratio, trop-T: troponin T

soning, the mean age of male patients was 29.3±13.2 years, while the mean age of females was 23.8±9.6 years [4] . In another study by Satar et al., the mean age for women was 24.5±10.1 years [5] , while it was 29.5±13.2 years for men. Our study was conducted in the adult emergency department and patients over the age of 18 were accepted. In this respect, our age data were found to be compatible with studies that included adult patients, while supporting the view that high-dose drug intoxication is a health problem that particularly concerns the young age group. The reason is that young adults are more prone to suicidal poisoning due to unemployment, difficulty in adapting to difficult living conditions and emotional traumas. In the studies, the rate of women in toxic dose drug intake was generally higher than men, and the ratio of women to men was 3 times higher. [6,7,8.] Similarly, in our study, the female-to-male ratio was found to be 3.8/1 (128/34 patients).

Studies showing the rate of high-dose drug intake in suicidal drug intake are few. In a study by Makk et al 498 (79.3%) of 628 patients were taking high-dose drugs, while 130 patients (20.7%) were taking non-high-dose drugs [9]. Similarly, in our study, 124 patients (77%) had high-dose drug intake, 25 patients (15%) were found to be taking non-high-dose drugs, and 13 (8%) patients were taking unknown-dose drugs. Considering these two studies, patients taking unknown doses of the medication will be considered as they received high doses of medication, and the treatment approach will be arranged accordingly. The types of drugs taken for suicidal purposes are the main indicator on the patient's clinic.

The types of drugs that cause poisoning vary in research. While sedatives and antiepileptics were the most common in the study of Anthony et al.[7] , NSAIDs were found most frequently in the studies conducted by Özköse et al. Paracetamol was found to be the most poisoning drug in many studies.[10-11]. In the study of Akkaş et al[12]. with 1,098 patients who applied to Hacettepe Adult Emergency Service between 1998 and 2002 with poisoning, it was reported that the highest number of poisoning cases was in the antidepressant group with a rate of 32%. In our study, drugs taken for suicidal purposes were at the top of our list with NSAIDs (21%), followed by paracetamol (20%), SSRI (17%) and TSAs (15%). As a result, it was considered that patients did not prefer any drug while taking drugs for suicidal purposes and took it randomly. NSAIDs, which have a wide range of use, have anti-inflammatory, analgesic and antiaggregant properties as well as many side effects. Various electrolyte disturbances have been detected in cases taking NSAIDs for suicidal purposes. In a study conducted by Wharam et al.[13]on triathlete athletes, a significant relationship was found between NSAIDs and hyponatremia. In a case reported by Roche et al.[14] hyponatremia was detected due to NSAID intake. However, in a study conducted by Page et al.[15] on 123 athletes, no significant difference in Na+ level change was found between those taking NSAIDs and the patients who don't take NSAIDs.

In our study, hyponatremia was found in 3 of 25 patients who took high-dose NSAIDs for suicidal purposes, and it was considered significant. In the few studies examining the relationship between potassium and NSAIDs; significant correlation was found between NSAIDs and elevated K levels. In our study, however, no significant K level change was detected in patients taking NSAIDs. When the previous studies and presentations were examined, it was determined that the patients who developed hyperkalemia were generally over the age of 50, had comorbidities, and were taking additional medication. The fact that the majority of the patients in our study were young may explain this different situation.

## Results

According to our suicidal study findings, the amount of drugs taken by our patients is not correlated with their blood levels. Although more than half of our patients have taken toxic doses of the drugs, most of the poisonings are mild and our results can not be generalized to severe poisoning cases. When the serum Na+ values of the patients who took and did not take high-dose NSAIDs were compared, it was found that the Na+ value changed statistically(p=0.000).

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Original Article
Eurasian Journal of Critical Care

# The Effect of "Tris-Hydroxymethyl Aminomethane" Treatment on Survival of Rats with Experimental Metabolic Acidosis Created by Intragastric Administration of Hydrochloric Acid "Tris-hydroxymethyl Aminomethane" Versus Acidosis

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## Abstract

**Background:** Treatment of acidosis is serious health problem within emergency departments and intensive care units etc. Ingestion of household cleaning solutions (due to both suicidal and accidental reasons) is still also a serious public health problem in Turkey and the most fatal complication thereof is, severe metabolic acidosis. An effective treatment should be provided for the cases presenting to emergency departments with life-threatening metabolic acidosis.

**Aim:** We aimed to compare the survival rate of rats with experimental metabolic acidosis created by intragastric administration of hydrochloric acid and treated with "tris–hydroxymethyl aminomethane" or normal saline solution alone.

**Study Design:** This was an experimental animal study.

**Methods:** Following ketamine-xylazine anesthesia, internal carotid artery of fourteen female Wistar albino rat was cannulated, basal blood samples were drawn and esophagus of each was cannulated with intracath. Hydrochloric acid was subsequently poured through the cannula towards stomach. After 30 minutes, blood gas status was checked in order to see if acidosis occurred or not. The rats which developed acidosis were randomly divided into "tris-hydroxymethyl aminomethane" and "normal saline solution" groups. Later the treatment with IV tris-hydroxymethyl aminomethane or normal saline was initiated. At 30$^{th}$ and 60$^{th}$ minutes of the treatment, pH, $PaO_2$, $HCO_3$, $PaCO_2$ and base deficit parameters were checked through arterial blood gas samples to monitor the efficacy of the treatment. At the end of the second hour of the study, the experiment was finalized and the survival of rats was documented.

**Results:** Following the development of experimental metabolic acidosis in rats by ingestion of intragastric hydrochloric acid, four rats in tris–hydroxymethyl aminomethane and six rats in normal saline group died prior to the end of the follow-up period.

This finding was statistically significant. There was no statistically significant difference between tris–hydroxymethyl aminomethane and normal saline groups with regard to body temperature, blood pressure, heart rate, $PaCO_2$ and $PaO_2$. However, the comparison of two groups with respect to survival indicated a significant difference ($p<0.05$). pH at 60th minute in tris–hydroxymethyl aminomethane group was significantly lower compared to that in normal saline group ($p<0.05$), and base deficit values at 30th and 60th minutes in tris–hydroxymethyl aminomethane group were significantly higher compared to that in normal saline group ($p<0.05$).

**Conclusion:** In this experimental rat model, we observed that treatment with IV tris–hydroxymethyl aminomethane prolonged the survival of rats with experimental metabolic acidosis created by ingestion of hydrochloric acid compared to the treatment with normal saline solution.

**Key words:** Metabolic acidosis, hydrochloric acid, tris–hydroxymethyl aminomethane, sodium bicarbonate

## Introduction

Treatment of the patients with acidosis is still a serious health problem within emergency departments and intensive care units etc. The main cause of acidosis may be due to different causes such as respiratory and/or metabolic causes (acute renal failure, diabetic keto-acidosis, uremic acidosis, etc.), suicidal cases (salicylate intoxication, methanol intake, ingestion of acidic solutions etc).

For cleaning of offices or houses, corrosive and acidic substances containing hydrochloric acid etc. are used frequently in daily life. Unfortunately, accidental or suicidal ingestion of these detersive and corrosive substances is still a serious health problem in many countries and as well in Turkey. Despite the presence of various precautions there against, accidental ingestion of these corrosive substances is mostly seen among children[1-5]. On the other hand, the reported adulthood cases occur a result of suicidal attempt since in Turkey, these substances are easily accessible in markets as packaged, but are stored in beverage containers in houses.

These acidic cleaners have both local destructive and systemic effects such as severe metabolic acidosis and these systemic effects are responsible for the mortality. In particular, the presence of acidosis affects the prognosis of the patient negatively[4,5]. Prompt and effective treatment should be provided for the patients admitting to emergency departments with life-threatening severe and deep metabolic ac-

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idosis clinic. Sodium bicarbonate ($NaHCO_3$) is the unique agent used to ameliorate the clinics of acidosis however; it has some side effects either such as hypernatremia or such as increased carbon dioxide ($CO_2$) retention etc. and the therapeutic effect of it is still doubtful [6-11].

In a study by Kazancı et al.[1] in a rat model with experimental metabolic acidosis created by ingestion of hydrochloric acid (HCl) intravenous $NaHCO_3$ treatment ended up with the shorten survival rate of rats.

In most of the studies regarding ingestion of corrosive substances, the regional damage to the gastrointestinal tract and complications related thereto as well as treatment options for such complications are discussed and emphasized.

There are only a limited number of clinical and experimental studies regarding life-threatening systemic effects brought by ingestion of acidic corrosive solutions. In such cases absorption of acid by tissue and the accumulation of lactic acid secondary to coagulation necrosis results with development of metabolic acidosis. When blood pH level declines to 7.10-7.20, myocardial muscle is suppressed and serious arrhythmias may occur[1,4]. Yanturali et al.[4] reported a case of acute ST segment elevated myocardial infarction associated with massive HCl ingestion. Severe systemic acidosis has developed and been complicated by the presence of acute myocardial infarction. In such cases, treatment specifically for increasing pH level is recommended with different alternative agents are also available for this purpose[11-17]. The absence of studies supporting treatment with $NaHCO_3$ in acidosis as well as the presence of publications showing the usefulness of alternative buffering agents like "Tris-Hydroxymethyl Aminomethane" (THAM) (Tribonat™, Fresenius, Kabi, Norway) are apparent in the literature. THAM is a biologically inert amino alcohol with a low toxicity and ability to buffer $CO_2$ and acids both in vivo and in vitro [6-10, 8-16, 18-23].

Here in this study, we aimed to investigate the effect of "THAM" treatment on survival of rats with experimental metabolic acidosis created by intragastric administration of HCL.

## Material and Methods

The experimental protocol of the present study was approved by the Local Animal Ethics Committee of the University of Dokuz Eylül, School of Medicine, and the study was carried out in the Multidisciplinary Experimental Animal Laboratory of the Dokuz Eylül University, Medical School. It was a joint multidisciplinary study participated by the Departments of Emergency Medicine, Anesthesiology and Intensive Care, and Laboratory Animal Science of the Dokuz Eylül University, Medical School.

## Animals

Fourteen female Wistar albino rats (weighing 210-250 g) with normal motor activities and 87% homogeneity from the Experimental Research Laboratory of the Dokuz Eylül University were included in the study. The subjects were kept under standard laboratory conditions (a constant lightning regimen providing a 12 hr light/dark cycle; 20-22°C room temperature; 50-60% humidity) with ad libitum access to water and food.

## Anesthesia and Surgical Interventions

Rats were intraperitoneally anesthetized with 35 mg/kg ketamine (Ketalar®, Pfizer, İstanbul, Turkey) and 5 mg/kg Xylazine (Xylazine Bio®, Pana-life Bio-Chemical, China). Anesthesia was maintained by intraperitoneally injected 20 mg/kg ketamine and 5 mg/kg xylazine at 90$^{th}$ minute of the experiment.

Following establishment of anesthesia, dorsal tail vein of rats was cannulated with a 24 G branula (B-CAT IV Kanül; Bıçakçılar Ltd. Şti., İstanbul, Turkey). The right common carotid artery of rats was cannulated with 24 G branula (Figure 1). Esophagus was subsequently exposed in the neck dissection region, and penetrated with the 24 G branula of which the end was moved towards the stomach. The branula was fixed inside the esophagus at a position with a distance of 0.1 cm from the inlet hole from where the branula was inserted into the esophagus. To prevent acid regurgitation, the front part of the platform on which rats were immobilized was uplifted by 45° (Figure 2). During these procedures, blood pressure, heart rate (Petaş KMA 250, İstanbul), and rectal body temperature of rats were monitored (May 9404-A Small Animal Temperature Controller).

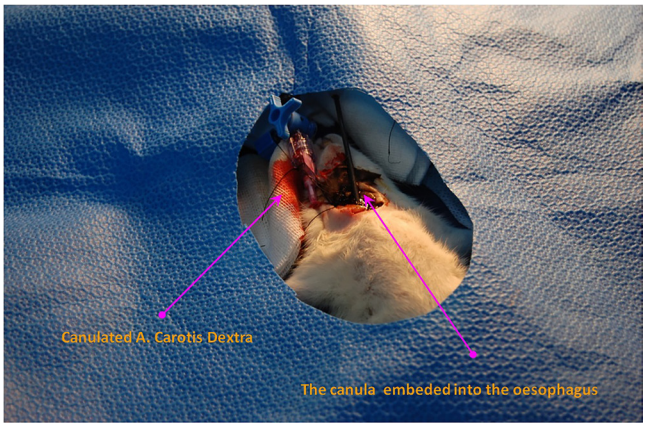


**Figure 1:** Rat with cannulated right common carotid artery and esophagus

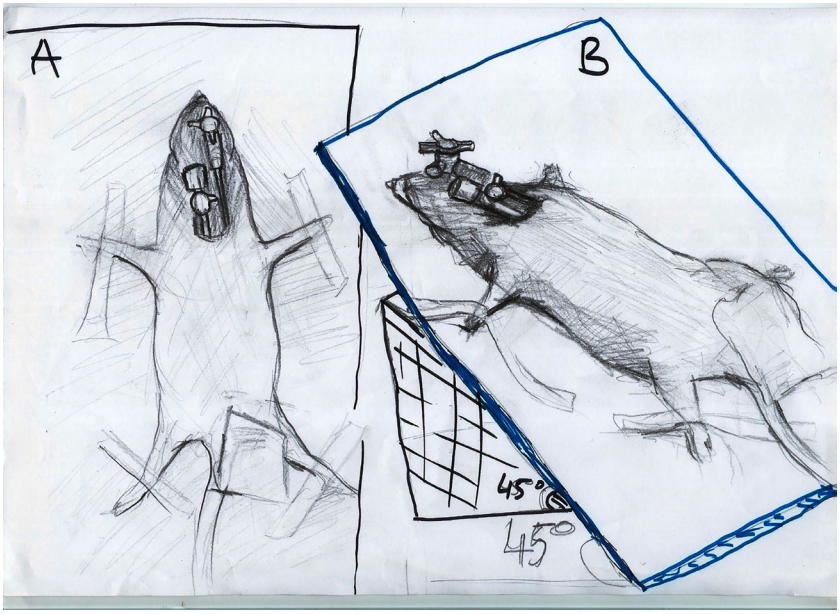


**Figure 2:** A) Rat with cannulated right common carotid artery and esophagus on a level surface
B) After the administration of hydrochloric acid to the esophagus, the platform was uplifted by 45° in order to prevent acid regurgitation.

## Acid Model

After the completion of surgical interventions as well as monitoring procedures, 0.3 ml of blood gas was drawn from the common carotid arteries of rats to check basal blood gas values. Thereafter, 4 ml/kg (1 ml/rat) of 18% hydrochloric acid (Tuz Ruhu, Viking Temizlik ve Kozmetik Ürünleri, İzmir, Turkey) was slowly injected via an injector towards the stomach through the cannula fixed in esophagus. Afterwards, the presence of acidosis in rats was checked with blood gas values observed 30 minutes after the administration of acid (Algorithm-1). The rats with acidosis were separated into two different groups for treatment.

1. **"THAM" (Treatment Group)** (n=8):
   Eight rats in this group were treated with intravenous infusion on average of 20-25 ml THAM. The dose of THAM was calculated with the formula of: "mmol of buffer = 0.3 x kg (body weight) x base deficit (mmol of hydrogen carbonate)". The resultant value was multiplied by 2 and converted into milligrams.

2. **"Normal saline solution" (Control Group)** (n=6) (control group was considered as n=6 due to death of two rat):
   Six subjects in control groups were treated with intravenous infusion of normal saline solution (NaCl 0.9%, Eczacıbaşı-Baxter Hastane Ürünleri San. ve Tic. A.Ş., İstanbul) 30 minutes after ingestion of the acid.

## Arterial Blood Gas Measurements

Prior to ingestion of acid (baseline) and at 30$^{th}$, 60$^{th}$ and 90$^{th}$ minutes after administration of acid, 0.3 ml of arterial blood samples from the pre-cannulated right common carotid artery of each rat were collected, and immediately examined for the pH, $HCO_3^-$, $PaO_2$, $PaCO_2$ and base deficit parameters with "Irma TRUPOINT Blood Analysis System" (Irma Trupoint Blood Analysis System ITC Med, USA).

## Timing and Method of Animal Sacrifice

At the end of the study, the surviving rats were sacrificed under high dose of halothane anesthesia.

## Statistical Analysis

SPPS for Windows 15.0 was used for statistical analysis. Results were calculated as mean ± standard deviation. For inter-group comparisons, Mann-Whitney U and Chi-square tests were used. For intra-group comparisons, Wilcoxon signed-rank test was used. Statistical significance was accepted at $p<0.05$.

## Results

There was no statistically significant difference between THAM and normal saline solution groups with regard to body temperature, blood pressure and heart rate (Mann Whitney U, p>0.05) (Table 1).

**Table 1:** Body temperature, heart rate and mean blood pressure

| | THAM group | Normal Saline Solution Group |
|---|---|---|
| **Body temperature (°C)** | | |
| Baseline | 36.7 ±0.59 | 36.9 ±0.2 |
| 30th minute | 37.0 ±0.1 | 36.9 ±0.2 |
| 60th minute | 37.0 ±0.1 | 37.0 ±0.1 |
| **Mean blood pressure (mmHg)** | | |
| Baseline | 76.9 ±15.2 | 65.3 ±13.7 |
| 30th minute | 96.1 ±27.7 | 98.8 ±21.8 |
| 60th minute | 82.1 ±18.9 | 81.9 ±19.0 |
| **Heart rate (beat/min)** | | |
| Baseline | 194.5 ±37.7 | 170.0 ±33.4 |
| 30th minute | 200.0 ±48.0 | 162.0 ±45.3 |
| 60th minute | 216.6 ±26.0 | 189.6 ±42.7 |

## Arterial Blood Gas Values

There was no statistically significant difference between THAM group and normal saline solution group with respect to blood pH values at baseline and at 30th minute. However, the mean pH value measured at 60th minute was significantly different (p=0.010). The mean pH values of normal saline group and THAM group at 60th minute were 6.87±0.29 and 7.18 ± 0.04, respectively (Table 2).

In comparison of mean $PaCO_2$ and $PaO_2$ values, no statistically significant difference was detected (Mann Whitney U, p>0.05) (Table 2).

There was no statistically significant difference between THAM group and normal saline group with respect to mean base deficit values at baseline (Mann Whitney U, p>0.05). However, at 30th and 60th minutes the difference between and normal saline groups for mean base deficit values was significant. The mean base deficit values of THAM group and normal saline group at 30th minute were 13.9±2.0 and 20.7±3.9, respectively (p=0.005). Besides, the mean base deficit values of THAM and normal saline groups at 60th minute were 9.62±0.61 and 24.6±6.8, respectively (p=0.003) (Table 2).

## Survival

The survival of rats in THAM group was significantly longer compared to that of rats in control group (p=0.013) (Table 3).

**Table 2:** Arterial blood gas values for THAM and Normal Saline solution groups

| | THAM Group | Normal Saline Solution Group |
|---|---|---|
| **pH** | | |
| **Baseline** | 7.36 ± 0.05 | 7.22 ± 0.05 |
| **30th minute** | 7.03 ± 0.12 | 7.03 ± 0.11 |
| **60th minute** | 7.17 ± 0.04 | 6.86 ± 0.28* |
| **$PaO_2$ (mmHg)** | | |
| **Baseline** | 76.6± 13.0 | 76.4 ±7.4 |
| **30th minute** | 65.1 ± 13.6 | 64.7 ± 10.6 |
| **60th minute** | 68.8± 12.8 | 82.5 ± 25.9 |
| **$PaCO_2$ (mmHg)** | | |
| **Baseline** | 44.0 ±9.4 | 41.2±11.6 |
| **30th minute** | 51.5 ± 9.5 | 41.3±11.9 |
| **60th minute** | 51.0± 9.0 | 47.0± 19.1 |
| **Base deficit** | | |
| **Baseline** | 3.6±2.8 | 2.7 ± 3.1 |
| **30th minute** | 13.9 ± 2.0 | 20.7 ± 3.9# |
| **60th minute** | 9.6 ± 0.6 | 24.6 ± 6.8# |

**Table 3:** Mean survival in "THAM" and Normal Saline solution groups

| | THAM Group | Normal Saline Solution Group |
|---|---|---|
| **Lifetime (in minutes)** | 114.5 ±30.5 | 67.0 ± 14.1 |

## Discussion

In the present experimental metabolic acidosis rat model created by intragastric administration of HCL, we found that the treatment with intravenous THAM decreased the mortality rate within the first 120 minutes compared to the control group treated with normal saline solution.

There is limited number of data about the effect of THAM on survival in the literature, but the potent buffering effect thereof is commonly emphasized [6-10, 12-14, 16-20, 22, 23]. Mortality following acid ingestion may be associated with the local or systemic effects of acid ingestion, or both[1]. We have merely focused on the systemic effects, so that this is the first and only study with such a design in the literature.

In our study, we used 18% HCL as the acidic agent, since this corrosive substance is widely used as a cleaning agent in houses and offices and can be accessed in almost every store in Turkey. Unfortunately, these substances are stored under inappropriate conditions and containers in houses, and in daily practice. They can be accidently ingested due to colorless, water-like appearance thereof. The local and systemic effects of the ingested corrosive substances on patients are among the serious causes of mortality.

For successful treatment of oral acid ingestion, the systemic and deep acidosis should be eliminated rapidly. In literature, there are a number of studies mentioning about the

effects of sulfuric and hydrofluoric acid. However, there are only a limited of number of studies on the effects of hydrochloric acid [1,5,9]). Nevertheless, there are also other publications indicating the efficacy of THAM administration for treatment of acidosis brought about by any factor (diabetic ketoacidosis; acidosis during cardiopulmonary resuscitation). In a paper of Taboada et. al., mentioned that their US military experience with THAM within their combat trauma population were unable to detect worse 30 day mortality associated with THAM administration [22]. On the other hand, we could not find any study regarding the effects of intravenous THAM for the treatment of acidosis experimentally created by acid ingestion on mortality in the literature.

The present study was fictionalized on a possible daily case. Accordingly, it was supposed that an individual accidently or intentionally (for suicide) drunk a corrosive substance presented to the emergency department within 30 minutes after the incident, and following the examination of patient, THAM treatment was initiated to ameliorate acidosis. For the design of this study we have benefited from two references[1,2]. In a study regarding the effects of $NaHCO_3$ and normal saline solution on mortality in an acidosis model, Kazancı et al.[1]) found that the treatment with $NaHCO_3$ increases the mortality. In that study, arterial blood gas values at 20$^{th}$, 40$^{th}$ and 140$^{th}$ minutes were checked to detect possible changes in metabolic table, and unlike the current literature, intravenous $NaHCO_3$, a known treatment method, was used for the treatment of acidosis.

Eray et al.[2] used an experimental rat model with nitric and hydrochloric acid, and showed the development of acidosis in rats 30 minutes after the administration of hydrochloric acid. Rats were followed-up for only 30 minutes and acidosis was not treated. Unlike the abovementioned studies, we planned to observe the effect of THAM treatment on rats with experimentally produced metabolic acidosis in the present study. THAM is a biologically inert amino alcohol with a low toxicity and ability to buffer $CO_2$ and acids both in vivo and in vitro. At 37°C, the pK (the pH value at which weak acids and bases in solutions are ionized by 50%) of THAM is 7.8, rendering it a more effective buffer than bicarbonate in the physiological range of blood pH. THAM is a proton acceptor. Stoichiometrically, each molecule captures one proton [6-7].

In our study, we observed that the pH in arterial blood gas at 60$^{th}$ minute in THAM group was significantly increased after acidosis. In a study carried out by Schneiderman et al.[13] with newborn piglets, THAM treatment has been shown to be effective in normalization of pH in respiratory acidosis. Also, in a study performed by Sirieix et al.[14] with albino rabbits, it was shown that THAM acts as a good buffer for correction of pH in acidosis in an isolated heart model, and a combination composed of bicarbonate and THAM gives even better results in correction of pH.

Kazancı et al.[1] didn't find any significant difference for pH values between normal saline solution and $NaHCO_3$ groups. Rehm et al.[19] showed that both $NaHCO_3$ and THAM increased the pH value in a study on comparison of $NaHCO_3$ and THAM in acidosis treatment. Similarly, Sun et al.[15] compared three different treatment approaches as $HCO_3$, Carbicarb and normal saline solution in a model of rats with respiratory and metabolic acidosis secondary to asphyxia, and recommended the use of Carbicarb for acidosis treatment instead of $HCO_3$ due to the observed insignificant increases in blood pH value in $HCO_3$ group. In a paper by Marfo et al.[10], it was concluded that THAM is a better buffering agent compared to $NaHCO_3$ for treating severe lactic acidosis since it generates serum bicarbonate and reduces the level of $CO_2$ in arterial blood.

In a study carried out in our clinic by Bolatkale et al.[11], we found that the treatment with THAM prolonged the survival of rats with metabolic acidosis created by intragastric administration of methanol compared to the treatment with $NaHCO_3$. In other words, the data obtained from our study was consistent with the present literature.

Although THAM is mentioned as an agent that have an ability to decrease blood $CO_2$ levels in conditions with impaired $CO_2$ excretion (such as acute respiratory distress syndrome and heart failure)[9-11,20], we observed a moderate increase in $CO_2$ levels following THAM treatment, and considered this moderate increase as mostly associated with respiratory factors given the time passing from the moment of drug administration to the moment of last observance for blood gas value. In a study regarding the effects of Carbicap, THAM and $NaHCO_3$ on dogs during cardiopulmonary resuscitation, Weinberger et al.[16] showed that THAM markedly decreased $CO_2$ levels. This finding is contrary to our findings. The method adopted by Bar-Joseph et al. was different from our study method, and the dogs in the study have been intubated and ventilated whereas the rats in our experiment have been allowed to breathe spontaneously. This contradiction may be the result of the abovementioned difference. According to Taboada, Tris-Hydroxymethyl Aminomethane (THAM) has been proposed as an alternative or adjunctive therapy for refractory acidosis in the setting of combat trauma. THAM is an amino alcohol that buffers carbon dioxide. It is a weak base that has been used as a buffering solution in various settings that have included respiratory failure, cardiac failure, renal tubular acidosis, brain injury, diabetic ketoacidosis, malignant hyperthermia, permissive hypercapnia, and drug intoxications [8,9,10,11,12,13]. THAM works by liberating native bicarbonate as a buffer to correct the patient's acidosis. THAM has a pH of 7.8, which makes it a more effective buffer than bicarbonate, the latter having a lower pH of 6.1[22]. In an experimental study done by Höstman et.al., of permissive hypercapnia in a porcine lung lavage model shows that intravenous infusion of THAM increased BE and bicar-

bonate concentration, normalized pH, and decreased PaCO2 during the infusion. After a prolonged infusion, however, pH decreased to values similar to those in controls owing to a rebound PaCO2 increase. Despite a similar low pH and a higher PaCO2 compared with controls, the PVR remained low in the THAM group. No major signs of augmentation of lung injury by THAM were found[23].

As a summary, we observed that the treatment with intravenous THAM decreased the mortality of rats within the first 120 minutes compared to the control treatment with normal saline solution.

## Conclusion

THAM is not available in the medical market of Turkey. We supplied the vials utilised in the present study with our own means from Norway. $NaHCO_3$ has been identified as an agent increasing mortality in acidosis treatment both in a study carried out in our clinic and some others, whereas THAM has been identified as an agent with an opposite effect in our study and also in anothers.

We anticipate that, if the same or similar results are obtained from the future studies on THAM with different models, the Ministry of Health, the Emergency Medicine Associations and the Professional Chambers by referring to our study may make it possible to import THAM for Turkey to be used for the treatment of patients with metabolic acidosis.

## Limitations of Our Study

1. Mortality following hydrochloric acid ingestion may be associated with the local or systemic effects of acid, or both. We have merely focused on the systemic effects. The relationship between the local effects of hydrochloric acid ingested accidently or intentionally and the mortality can be examined in a further study.
2. In our study, rats were allowed to breathe spontaneously. We could have preferred to get the respiration of rats under control by intubation, thereby excluding the role of respiration in development of acidosis.
3. We have merely focused on the systemic effects, so that this is the first and only study with such a design in the literature. The relationship between the local effects of acid ingested accidently or intentionally and the mortality can be examined in a further study.

## Acknowledgement

We would like to thank to Çiğdem Akalın Akkök, MD, PhD from the Department of Immunology and Transfusion Medicine, Section of Immunohematology, Oslo University Hospital, Ullevaal, Oslo, Norway for helping us to obtain the vials of tris-hydroxymethyl aminomethane (Tribonat™) from Norway, since it is unavailable in the medical market of Turkey.

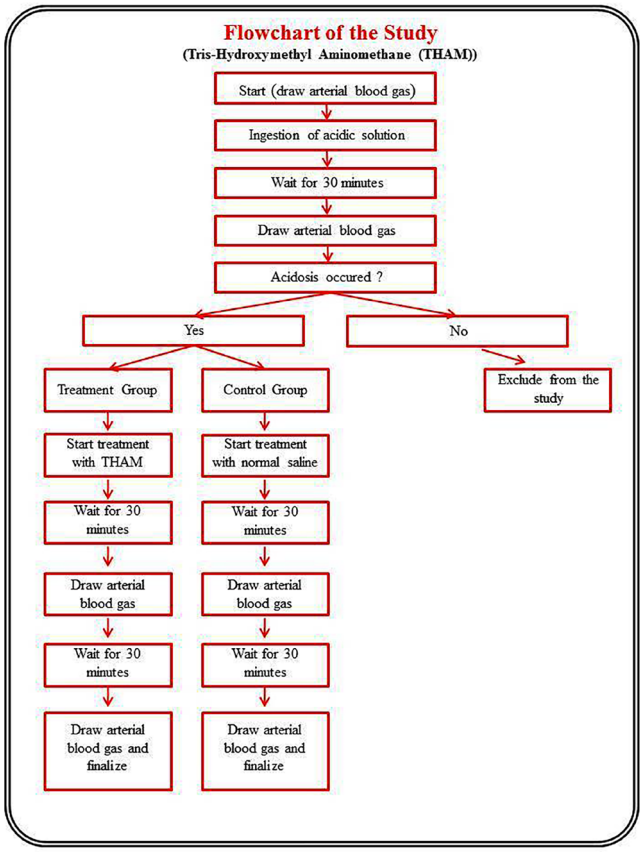


**Figure 3:** Flowchart of the study

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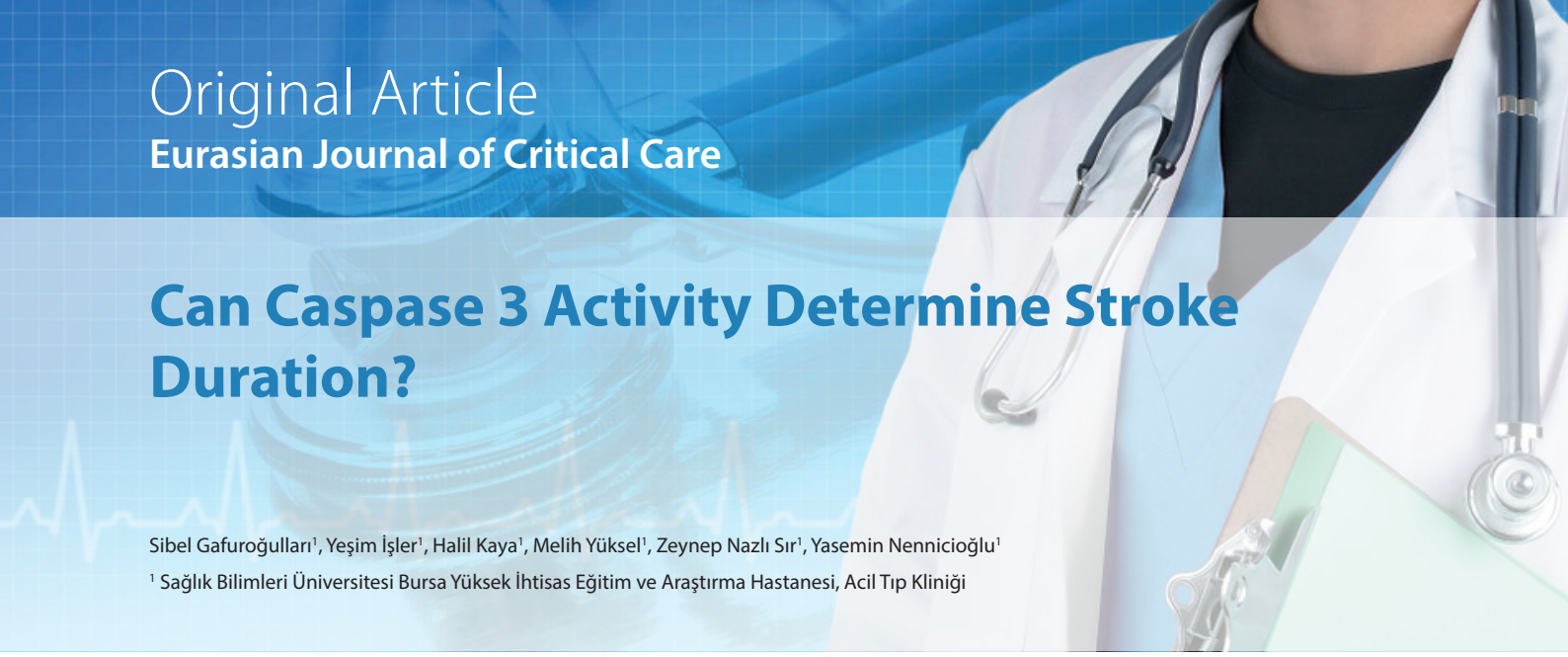

# Can Caspase 3 Activity Determine Stroke Duration?

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## Introduction

Stroke is one of the most important emergencies in neurological diseases. Ischemic stroke has an important place among emergency department admissions. One of the most important questions in assessing the thrombolytic treatment suitability of patients is to know the onset duration of stroke. Door - needle time for thrombolytic therapy is 4.5 hours. Therefore, time is very important for thrombolytic treatment. If there is no any person present with the patient at the time of stroke, or stroke occurred while asleep, the patient loses the chance of thrombolytic therapy because the onset duration of stroke is unknown. Despite the emerging technology and many biochemical parameters for such patients, a biomarker that still provides information about time has not been found.

Depending on the duration and severity of ischemia, necrosis or apoptosis, or both, may cause death of brain cells[1]. Apoptosis is a programmed, organized cell death process. Activation has been described after brain ischemia[2]. Apoptosis occurs after a complex caspase cascade that results in DNA fragmentation, in which Caspase 3 plays a critical role in the final stage. However, other Caspaz-3-independent mechanisms have been described to occur in the ischemic penumbra and are also associated with neuronal apoptosis. Caspase-3 is synthesized as procaspase. Apoptotic cell death in neurons returns to the active form in the cascade. Neuronal cell death as a result of experimental ischemia and traumatic brain injury occurs when caspase-3 is activated. There are many methods used in the determination of apoptosis in tissue. Identification of caspase 3 expressing cells is one of these methods[3]. In animal studies, caspase inhibitors have been used to reduce neuronal damage[4]. In animal models of focal cerebral ischemia, apoptotic cells have been shown to increase Caspase 3 activity and decrease infarct width with Caspase 3 inhibition[5]. Caspase 3 deficient rats were found to be more resistant to ischemic stress[6].

Only a few studies have been associated with Caspase 3 in caspase-associated apoptosis in ischemic brain tissue in humans. Based on this information, we designed our study to investigate the relationship between Caspase 3 level and stroke duration, which we measured from patients with known stroke onset, and to estimate the stroke onset.

## Materials and Methods

This study was conducted with the approval of Clinical Research Ethics Committee of Uludağ University, Faculty of Medicine dated 05.12.2017, numbered 52588837-000 / 659.

Between December 2017 and April 2018, patients with a diagnosis of acute ischemic stroke, known to have an onset of acute ischemic stroke, were included in the study at Bursa Yüksek Ihtisas Training and Research Hospital, Emergency Medicine Clinic. The control group included volunteers over 18 years of age, no history of chronic disease, infectious or inflammatory disease, who agreed to participate in the study, and had a similar age distribution to stroke. Under the age of 18, unknown stroke onset time, the patients who had a stroke during sleep, history of previous stroke or lacunar infarction, hemorrhagic stroke, transischemic attack or seizure, history of malignancy, infectious process and could not the patients information were excluded.

During the study, 1233 patients were diagnosed as stroke and 246 of them were evaluated as hemorrhagic stroke. The remaining 987 patients were diagnosed with ischemic stroke. When 100 of these patients met the inclusion criteria, our study was terminated.

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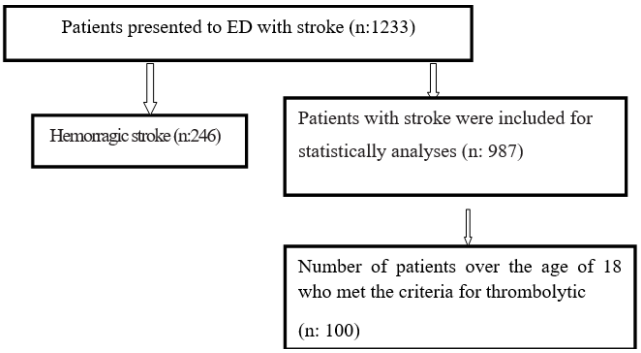


**Figure 1:** Flow chart of patients

## Study Planning

The study was conducted prospectively in patients admitted to Bursa Yüksek Ihtisas Training and Research Hospital Emergency Department and diagnosed as acute ischemic stroke. 55 female, 45 male patients and 27 female and 23 male controls were included in the study. Demographic characteristics, smoking and duration of the patients, hypertension, diabetes mellitus (DM), coronary artery disease, rhythm disturbances and other chronic diseases were recorded. Drugs used by the patient were also recorded. The NIHSS (National Institutes of Health Stroke Scale) score was calculated for each patient and the time of occurrence of stroke was recorded.

Blood was collected from each patient who agreed to participate in the study at the time of admission for other analyzes, and 5 ml of blood was collected into the tube containing separator gel and the time from the onset of stroke to the collection of blood was recorded as stroke time.

Stroke times were divided into three groups. Patients who applied within the first 30 minutes were enrolled in the 30th minute group. The arrivals between 3-4 hours were recorded in the 4th hour group and the arrivals after 4 hours were recorded in the> 4,5th hour group. Stroke times were divided into two groups. Patients who applied the first the arrivals were recorded in the 4th hour group and the arrivals after 4 hours were recorded in the> 4,5th hour group.

Blood was centrifuged. The obtained serum was taken into eppendurf tubes and stored at -20°C. Total Caspase 3 levels were measured in the biochemistry laboratory of our hospital (standard range 0.31-20 ng / mL) following the manufacturer's instructions by ELISA method. Blood samples were taken from healthy volunteers in the control group and Caspase 3 level was recorded.

All patients included in the study underwent tomography. Patients with bleeding on tomography were excluded from the study. MRI was not performed in all patients because of thrombolytic or thrombectomy procedure. Data on the involved side, ischemia-inducing vessel and ischemic brain tissue volume of patients with MRI were recorded, and patients without MRI were not subjected to these analyzes. 1.5 T Sıgna Excite GE Magnetic Resonance System was used for MRI imaging. Exponential ADC images were used for volume measurement to determine infarct areas with greater accuracy.

Volumetric images are obtained from selected Exponential ADC images on selected patients, using three dimensional imaging models, on a point-by-point basis and optimal calibration, with paint, using a detailed modeling system to measure volumes in four planes: oblique, axial, sagittal and coronal. The volume of ischemic tissue was extracted. The volume area of the infarcted tissue resulting from this extraction was obtained in three dimensions on the calculations of the machine. The measurement was performed by a radiologist.

## Statistical Analysis

In summarizing the data obtained from the study, descriptive statistics were given in tables as mean ± standard deviation or median - quartile width for continuous variables. Categorical variables were summarized as numbers and percentages. Normality test of numerical variables was checked by Kolmogorov Smirnov Test. Mann Whitney U Test was used for comparison of two independent groups when numerical variables were not normally distributed. Kruskall Wallis Test was used for independent comparisons of more than two groups. Pearson Chi-Square was used in 2x2 tables and Fisher Freeman Halton Test was used in RxC tables. Spearman Rho Correlation Coefficient was used to investigate the relationships between numerical variables when the variables were not normally distributed. In statistical analysis, Jamovi Project (2017) (Jamovi (Version 0.8) [Computer Software] was used and statistical significance was considered as 0.05 (p-value). In the comparison of two independent groups, t test was used for the Independent Groups, which is a parametric test, and Mann Whitney U test was used in cases where the numerical variables showed normal distribution.

## Results

In table 1 gender, age and caspase 3 levels of stroke patients and control groups were compared and no significant difference was found.

In table 2, risk factors and caspase 3 level were compared and no significant difference was found.

In table 3, stroke patients were evaluated for the NIHSS score, caspase 3 levels, stroke onset duration, stroke occurence time, ischemic volume, affected artery, affected side and MR imaging. Since some of the patients included in the study were thrombolytic or thrombectomy candidates because of a stroke unit in our hospital, MRI was not performed for each patient. It was seen that 55% of the patients underwent MRI and 45% did not undergo MRI.

In table 4, caspase 3 median values was compared with stroke side, level of consciousness, speech impairment, upper extremity weakness, lower extremity weakness, and facial paralysis. When the comparisons were examined, the difference between Caspase 3 median values only according to the presence or absence of facial paralysis was statistically significant (p = 0.033). The median of those without facial paralysis was higher than those with facial paralysis. When the other comparisons were examined, it was found that the difference between the median values was not statistically significant.

In table 5, relationship between stroke occurrence time and NIHSS Score and stroke onset duration were compared and no significant difference was found.

In table 6, relationship between stroke onset duration and ischemic volume, NIHSS score and caspase 3 values were compared and no significant difference was found.

## Discussion

The aim of this study was to investigate whether there is a relationship between Caspase 3 levels and stroke duration obtained from patients with acute ischemic stroke symptoms and to predict the time of stroke for patients whose stroke time is not determined based on Caspase 3 level. Thus, it was aimed to determine whether stroke patients with thrombolytic indication but not thrombolytic stroke could not be identified because stroke time is not known. At the same time, since Caspase 3 is an apoptosis enzyme, it is aimed to investigate whether there is an association between ischemic brain volume and the relationship between NIHSS score and Caspase 3 which measures the clinical severity of stroke.

Male gender ratio was 45%, female ratio was 55% and the mean age was 68.57 ± 13.25. There was no statistically significant difference between the mean age and sex between the patients and the control group. In the literature, male dominance in stroke patients has been shown in many studies, but in our study the rate of women was found to be higher. In a study by Jesper et al., the rate of male was 54% and female was 46% [7]. In the study of Bustamante et al., the rate of male patients was 53.9%, female patients was 46.1%, and the average age was 70[8].

In a study by Rosell et al., no significant relationship was found between Caspase 3 levels and risk factors other than atrial fibrillation. In stroke patients with atrial fibrillation, Caspase 3 level increased in the first 24 hours[9]. In another study by Montaner et al.,the etiology of biochemical markers and stroke was investigated and caspase 3 levels were found to be significantly higher in patients with AF[10]. In our study, we found no possible increase in Caspase 3 in the late period because we looked at Caspase 3 levels in the early hours. In our study, no statistically significant relationship was found between the risk factors and Caspase 3 levels. When the patients included in the study were grouped based on stroke duration, no correlation was found between Caspase 3 level and stroke duration.

In a study by Koç et al., patients aged 65 years or older who presented to the emergency department with neurological symptoms were examined for their final diagnosis. In their study, the most frequent presenting complaint was speech disorder with a rate of 37.5%. hemiparesis 2.9%; facial paralysis was found to be 1 % [11].The most common finding in our study was speech disorder with a rate of 62 %, and 15 % change in consciousness and 49 % facial paralysis. No significant correlation was found between these neurological findings and Caspase 3 activity except for patients with facial paralysis. The median Caspase 3 levels of the patients with facial paralysis were lower than those without facial paralysis.

When the duration of admission to the emergency department was evaluated, it was observed that 66% of the patients presented before 4.5 hours. In the study performed by Kıyan et al., the application rate was recorded as 20.5% in the first three hours[12].Their study was carried out in 2009. During the 9-year period, ambulance services have been developed in our country, training on stroke has been increased and awareness on stroke has increased. In addition, since our hospital had a stroke unit, it was suggested that the patients could be brought to the emergency room by ambulance in the early period.

In the present study, 74% of the patients had a stroke between 06:00 and 18:00 in the evaluation of stroke time zone. In a study by Kıyan et al., 60.5% of the patients were admitted between 18:00-08:00, the most common application time was between 18:00-21:00 and 22: 00-01:00[15]. In our study, it is seen that the majority of the patients came to the emergency department between 06:00-18:00. The reason for this time may be that the ambulance is called and the patient is informed about the clinical change as soon as there are signs of stroke, as the hours in which the patient and his relatives are together are within this interval.

There was no significant difference between the time zone of stroke and the NIHSS score of the patients. In addition, a statistically significant result was not obtained in the comparison between the time of emergency admission and the time zone where the stroke occurred.

MRI was performed in 55% of the patients in our study group. 56.36% of the patients had left side of the brain, 34.55% right and 9% had bilateral involvement. The ischemic areas detected in the evaluation were detected as MCA involvement with a rate of 50.91%. In the study performed by Morita et al., MCA was the most commonly affected artery[13]. In our study, the most affected MCA infarction was observed similar to the rates in the literature.

The mean value of ischemic tissue volume obtained from Exponential ADC maps of the patients included in the study and MRI was calculated as 4.78 $cm^3$. In the study of Youn et al. ischemic brain tissue volume was found to be 3.91[14].

The mean NIHSS score of the patients in our study was 7.9. In the study of Appelros et al., the average NIHSS score was found to be 6[15]. When the ischemic tissue volume and NIHSS score of our patients were compared, a significant, linear and same-way relationship was observed. In the study of Morita et al., the relationship between ischemic volume and NIHSS could not be established[13].

In a study by Linfante et al., no correlation was found between NIHSS score and lesion volume, and it was thought that the study was due to the fact that the study was performed on patients with posterior circulation stroke[16].

Caspase 3 increased after ischemia in ischemic human brain tissue[17]. In the study performed by Montaner et al to determine the biochemical marker in the differential diagnosis of acute stroke, Caspase 3 level was found to be the most predictive marker[18].

Animal models of cerebral ischemia have been shown that in the first 24 hours after ischemia, Caspase 3 is activated early in apoptotic cells on the border of ischemic infarction[19]. It was found that Caspase 3 is rapidly activated with neuronal death due to apoptosis in ischemic brain tissue[20]. In studies conducted in patients with ischemic stroke, Caspase 3, an apoptosis enzyme, was found to be higher in stroke patients than in control groups[9]. In animal studies, Caspase inhibitors have been used to reduce neuronal damage[4]. In animal models with focal cerebral ischemia, Caspase 3 activity is increased in apoptotic cells and Caspase 3 inhibition has been shown to decrease infarct width[5]. Caspase 3 deficient rats were found to be more resistant to ischemic stress[6]. However, most of these studies are animal model studies. It was found that Caspase 3 is rapidly activated with neuronal death due to apoptosis in ischemic brain tissue[20]. In 2004, Qi et al. conducted a study investigating the relationship between neuron injury and Caspase 3 in ischemia in the human hippocampus. Immunohistochemical method was used and Caspase 3 increased slowly after 8 hours, showed a dramatic increase after 24 hours and started to decrease after 72 hours[21]. Lynch et al. conducted a series of caspase measurements to investigate a diagnostic test for acute stroke. In the first three hours after the onset of stroke, the mean Caspase 3 level was 10.9 ± 3.9 ng / mL; 18.2 ± 9.8 hours in 3-6 hours; the mean 39.6 ± 18.6; it was measured as 88.9 ± 33.6 in 12-24 hours on average[22].

Based on the findings in the literature, we can interpret the reason for the difference between the patients in our study and the control group because the majority of our patients were measured before 4.5 hours. Our aim was to investigate the level of Caspase 3 in patients admitted for the first 4.5 hours of thrombolytic therapy and whether this would give an idea about infarction. Perhaps there would be a marked increase in the Caspase 3 level in our patients in the following hours.

In our study, no statistically significant difference was observed between Caspase 3 activity and the control group ($p = 0.556$). In the study conducted by Rosell et al., the median Caspase 3 level obtained from the stroke group was 1.66 ng / ml, and 1.08 ng / ml in the control group, and the difference between the two groups was found to be significant[9]. In a study by Montaner et al., caspase 3 and nine other biomarkers were used to differentiate between stroke and other neurological events mimicking the stroke clinic. It was concluded that the combination of caspase 3 and D-dimer was the strongest predictor of stroke[23].The data of our study did not support these findings. On the other hand, Bustamante et al. compared the Caspase 3 level with ischemic stroke, hemorrhagic stroke and other diseases that mimic stroke and found no significant difference between them[8].

In a study by Montaner et al., it was concluded that there was no significant relationship between caspase 3 and NIHSS score[10]. Similarly in our study, no significant correlation was found between Caspase 3 level and NIHSS score.

In the study performed by Rossel et al., repeated caspase 3 levels were measured from stroke patients and control diffusion MRI images were obtained and it was found that caspase 3 levels were increased in patients whose infarct area increased compared to the first MRI image[9]. In our study, no significant relationship was found between caspase 3 levels and ischemic brain tissue volume calculated from MRI images of stroke patients. This may be due to the fact that the Caspase 3 level was examined in the early period rather than in the late period. (before 4.5 hours)

In our study, we evaluated the patients in two groups according to the stroke onset period before and after 4.5 hours. There were no significant difference between the groups in terms of NIHSS scores, ischemic brain tissue volume and Caspase 3 levels.

Our aim was to determine whether the patient was in the time zone where we could use thrombolytic therapy based on Caspase 3 level. But our research has not found such a relationship.

## Limitations

We included patients with known stroke duration in our study. Since these patients are mostly brought to the hospital in less than 4.5 hours, we think that blood samples taken from these patients before there is a significant increase in Caspase 3 levels may be the reason for the low levels in our cases. The fact that we have not repeatedly investigated caspase 3 levels can be considered as a limitation in this regard.

## Conclusion

In our study, caspase 3 levels were not significant in terms of both the presence or absence of stroke and the duration of stroke onset. The caspase 3 level is not useful for early detection of ischemic stroke duration for thrombolytic treatments.

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Orginal Article
Eurasian Journal of Critical Care

# A Comparison of The Glasgow-Blatchford Score And Pre - Endoscopic Rockall Score Systems To Predict Clinical Outcomes in Patients With Upper Gastrointestinal Bleeding

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## Abstract

**Objectıve:** Acute upper gastrointestinal system bleeding in patients presenting at the Emergency Department is a significant cause of morbidity and mortality. Different scoring systems have been developed for the evaluation in emergency department of patients with gastrointestinal system bleeding. Emergency endoscopy may not be possible in patients presenting to the emergency department with gastrointestinal bleeding. The aim of this study was to compare pre – endoscopic scoring systems (Like the Glasgow Blatchford Score and the pre -endoscopic Rockall scoring systems) in patients presenting at the emergency department with upper gastrointestinal system bleeding, to determine high-risk patients and examine the efficacy of these systems in predicting 30-day mortality.

**Method:** This prospective study included patients aged >18 years who presented at the Emergency department of XXX Training and Research Hospital between January 2014 and December 2014.

**Results:** The study included a total of 101 cases with a mean age of 65.62 years (range, 19-97 years). Melena was determined in 45 (44.6%) patients, hematochezia in 25 (24.8%), hematemesis in 26 (25.7%), diarrhea and abdominal pain in 7 (6.9%) and syncope in 1 (1.0%). The mean Blatchford score of the patients was 10.56±3.75 (range, 3-19). According to this scoring system, 6 (5.9%) patients were at moderate risk, 18 (17.9%) at high risk, and 77 (76.2%) at very high risk. The mean pre – endoscopic Rockall score was 3.11±2.37 (range, 0-9). According to this scoring system, 49 (48.5%) patients were at low risk, 22 (21.8%) at moderate risk, and 30 (29.7%) at high risk.

Of the 49 cases identified as low risk with the pre- endoscopic Rockall classification, 4 were classified as moderate risk, 14 as high risk, and 31 as very high risk using the Blatchford scoring system. Of the 22 cases identified as moderate risk with the pre- endoscopic Rockall classification, 1 was classified as moderate risk, 2 as high risk, and 19 as very high risk using the Blatchford scoring system. Of the 30 cases identified as high risk with the pre – endoscopic Rockall classification, 1 was classified as moderate risk, 2 as high risk, and 27 as very high risk using the Blatchford scoring system. The differences between the two scoring systems were determined to be statistically significant.

No statistically significant difference was determined between the mortality rates of cases according to the Blatchford scoring ($p>0.05$). The difference between the mortality rates of the cases according to the pre – endoscopic Rockall scoring was determined to be statistically significant ($p=0.001$, $p<0.01$). The mortality rate of patients at high risk according to the pre – endoscopic Rockall scoring was determined to be higher. The difference between the mortality rates of the cases at high risk according to the pre- endoscopic Rockall scoring was determined to be statistically significant ($p=0.001$, $p<0.01$). The risk of mortality was determined to be 6.022-fold greater in cases at high risk according to the pe - endoscopic Rockall scoring. The odds value for pre-endoscopic Rockall scoring was 6.022 (95% CI: 2.148-16.882).

**Conclusion**: The Blatchford and pre- endoscopic Rockall scoring systems were not seen to be consistent with each other and in the prediction of mortality, pre- endoscopic Rockall scoring was determined to be better.

**Key words:** Emergency Department, Gastrointestinal bleeding, pre- endoscopic Rockall scoring system, Glasgow-Blatchford scoring system

## Introduction

Upper gastrointestinal bleeding is defined as bleeding that originates proximal to the Treitz ligament. When evaluating the patient, stabilisation must be applied at the same time as the classic physical examination, taking the medical history and laboratory tests[1].

Risk evaluation before endoscopy, which can be evaluated during the first presentation in emergency department (ED), is based on clincal and laboratory parameters. Rapid evaluation of these provides a great advantage. These systems before endoscopy include the pre- endoscopic Rockall (pRS) and Blatchford (GBS) systems[2]. The Rockall system before endoscopy is based on the patient age, comorbidities and blood pressure values. The Blatchford system does not consider the age, but includes basic laboratory tests, such as urea and hemoglobin levels. The purpose of this is prediction before the need for any intervention[3,4]. If risk evaluation is made during endoscopy, endoscopic signs are examined. These signs are determinants of the subsequent clinical course and endoscopic intervention. The combination of clinical, laboratory and endoscopic data is used in the risk scores after endoscopy.

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The Rockall (Total Rockall) score after endoscopy is widely used. When these scores are compared with the pre-endoscopy scores, they are more appropriate for the prediction of re-bleeding and mortality. The use of information provided by endoscopy has a significant advantage, but there is also the disadvantage of a delay in the results as it is performed after endoscopy[5].

The aim of this study was to determine the most effective scoring system by comparing the risk scores frequently used in patients with upper gastrointestinal system (GIS) bleeding.

## Material – Method

Approval for this prospective cross-sectional study was granted by the Local Ethics Committee. The study was conducted in the Emergency Department (ED) of XXX Training and Research Hospital between January 2014 and December 2014. In this period, a total of 101 patients aged >18 years presented at the ED, and as a result of examinations and tests were diagnosed with upper GIS bleeding. For each patient, the Blatchford and pre- endoscopic Rockall scores were calculated. For various reasons, endoscopy was not applied and as it was more practical to apply the pre- endoscopic Rockall scoring in the ED, this was used rather than the total Rockall score. These two scores were compared in respect of determining the mortality risk.

## Statistical Analysis

Data obtained in the study were analysed statistically using NCSS 2007 software (Number Cruncher Statistical System, Kaysville, Utah, USA). Descriptive statistical methods were stated as mean±standard deviation, median, minimum, maximum values or number(n) and percentage (%). In the comparison of qualitative data, the Pearson Chi-square test, Fisher-Freeman-Halton Exact test and Fisher Exact test were used. In the evaluation of the levels of the Blatchford and pre- endoscopic Rockall scores able to determine mortality, diagnostic screening tests (sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]) were used. A value of $p<0.05$ was accepted as statistically significant.

## Results

Between January and December 2014, evaluation was made of a total of 101 patients, comprising 60 (59.4%) males and 41 (40.6%) females with a mean age of 65.62±18.85 years (range, 19-97 years).

Mean systolic blood pressure was determined as 106.25±19.97 (range, 50-180), mean diastolic blood pressure as 66.97±13.52 (30-100) and mean pulse measurement was 92.99±17.05 (range, 50-145).

The complaints of the patients on presentation were melena in 45 (44.6%) patients, hematochezia in 25 (24.8%), hematemesis in 26 (25.7%), diarrhea and abdominal pain in 7 (6.9%) and syncope in 1 (1.0%) (Figure 1).

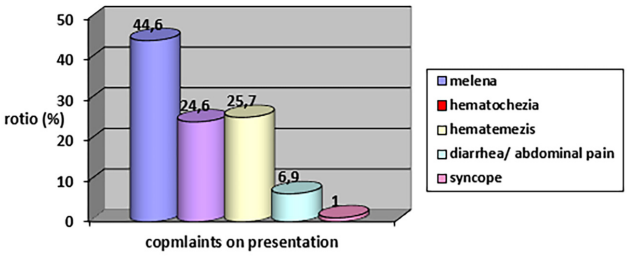


**Figure 1:** Complaints on presentation

The mean hemoglobin value was 9.64±2.80 (range, 3.6-16.1), with a value <8 determined in 30 (30.3%) patients and ≥8 in 69 (69.7%) patients.

The mean PLT value was 262.25±143.63 (range, 3.4-838). The mean MPV (mean platelet volume) measurement was 8.48±2.21 (range, 5.1-16.6) and mean INR measurement was 1.55±1.53 (range, 0.9-10.3).

A total of 97 (96.0%) patients were hospitalised for treatment; 4 (4.0%) were admitted to the Intensive Care Unit (ICU) and 93 (92.1%) to the wards. Endoscopy was applied to 77 (76.2%) patients, re-bleeding was seen in 1 (1.0%) patient, and comorbidities were seen in 91 (90.1%).

Mortality developed in 21 (20.8%) patients.

The mean Blatchford score of the patients was 10.56±3.75 (range, 3-19). According to this scoring system, 6 (5.9%) patients were at moderate risk, 18 (17.9%) at high risk, and 77 (76.2%) at very high risk.

The mean pre- endoscopic Rockall score was 3.11±2.37 (range, 0-9). According to this scoring system, 49 (48.5%) patients were at low risk, 22 (21.8%) at moderate risk, and 30 (29.7%) at high risk (Figure 2).

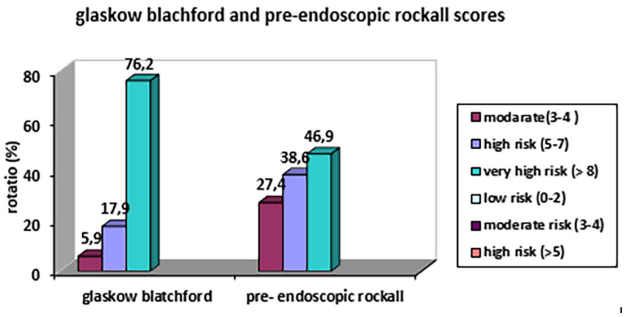


**Figure 2:** Blatchford and pre – endoscopic Rockall scores

Of the 49 cases identified as low risk with the pre – endoscopic rockall classification, 4 were classified as moderate risk, 14 as high risk, and 31 as very high risk using the Blatchford scoring system.

Of the 22 cases identified as moderate risk with the pre – endoscopic Rockall classification, 1 was classified as moderate risk, 2 as high risk, and 19 as very high risk using the Glaskow Blatchford scoring system.

Of the 30 cases identified as high risk with the pre – endoscopic Rockall classification, 1 was classified as moderate risk, 2 as high risk, and 27 as very high risk using the Blatchford scoring system.

Accordingly no statistically significant compatibility was determined between the two scoring systems (Kappa: 0.046; p:0.322; p>0.05).

No statistically significant difference was determined between the mortality rates of cases according to the Blatchford scoring (p>0.05). The difference between the mortality rates of the cases according to the pre – endoscopic Rockall scoring was determined to be statistically significant (p=0.001, p<0.01). The mortality rate of patients at high risk according to the pre – endoscopic Rockall scoring was determined to be higher. No statistically significant difference was determined between the mortality rates in cases at high and very high risk acccording to the Blatchford scoring (p>0.05).

The difference between the mortality rates of the cases at high risk according to the pre – endoscopic Rockall scoring was determined to be statistically significant (p=0.001, p<0.01). The risk of mortality was determined to be 6.022-fold greater in cases at high risk according to the pre – endoscopic Rockall scoring. The odds value for pre – endoscopic Rockall scoring was 6.022 (95% CI: 2.148-16.882) (Figure 3).

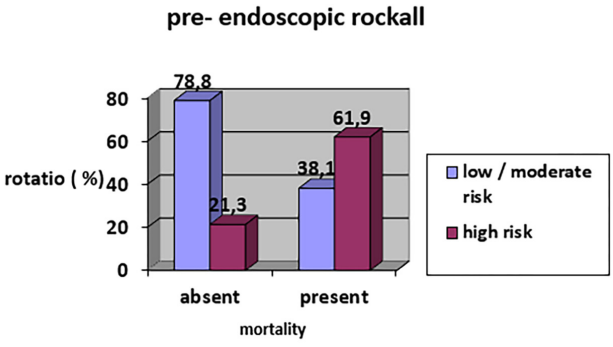


**Figure 3:** Mortality rates according to the pre – endoscopic Rockall scoring

According to the presence of mortality, those at high and very high risk (≥5) in the Blatchford scoring, sensitivity was 90.48%, specificity 5%, PPV 20%, NPV 66.7% and accuracy was 22.77%. In the ROC obtained, the area under the curve (AUC) was determined as 47.7% and standard error as 7.3%, which was not found to be statistically significant (p>0.05).

According to the presence of mortality, those at high and very high risk (≥5) in the pre – endoscopic Rockall scoring, sensitivity was 61.90%, specificity 78.5%, PPV 43.33%, NPV 88.73% and accuracy was 75.25%. In the ROC obtained, the AUC was determined as 70.3% and standard error as 6.8%. This area was found to be statistically significant (p<0.01).

The Glaskow Blatchford and pre – endoscopic Rockall scoring systems were not seen to be consistent with each other and in the prediction of mortality, pre – endoscopic Rockall scoring was determined to be better.

## Discussion

Acute upper GIS bleeding is frequently encountered in ED as a cause of morbidity and mortality, and is responsible for 500,000 hospital admissions per year in the USA. The annual incidence is up to 165 per 100,000. Despite developments in medical treatment, ICU management, endoscopy and surgical fields in the last 20 years, mortality remains at approximately 13%-14% [6]. As for every disease, for the proper management of patients with GIS bleeding, correct grouping in respect of recurrence and mortality is necessary. The categorisation of low and high risk patients on presentation is important. When patients are classified according to severity, the management of GIS bleeding patients is more effective and morbidity and mortality are reduced[7].

An ideal scoring system determines acute upper GIS bleeding and should be able to differentiate between low risk and high risk patients who may develop repeated bleeding and mortality. Several scoring systems have been developed in recent years to be able to differentiate patients who should be hospitalised for the application of aggressive treatment and patients who can be treated as outpatients. Of these, the Rockall score (RS- pre-endoscopic RS), Total RS (including endoscopic findings) and the Glasgow Blatchford score are systems used in ED to classify patients presenting with upper GIS bleeding[8, 9]. There are several reasons for upper GIS bleeding, and these reasons often show differences depending on the age of the patient. However, gastric and duodenal ulcer hemorrhages account for three-quarters of all cases. Accordingly, patients often present at ED with complaints of hematochezia and melena[10]. The complaints on presentation of the patients in the current study were seen to be consistent with findings in literature (Figure 1). There are several studies in literature related to upper GIS bleeding, and the common point of these studies is that one of the most important factors affecting mortality is re-bleeding[2, 8].

The Rockall scoring system gives an idea about the probability of mortality. The Rockall score is formed of three non-endoscopic measurements (age, shock, comorbidities) and two endoscopic measurements. This system was developed from a prospective study by Rockall et al which evaluated independent risk factors for mortality in

4185 cases of acute upper GIS bleeding and the subsequent prospective evaluation of another group of 1625 patients in the same study. Rockall et al attempted to predict mortality with simple variables. According to the study, in patients with a score of 0-1-2, the risk of re-bleeding is <5% and thus there is a low probability of mortality. In the moderate risk group of those with a score of 3-4, the risk of mortality is increased approximately 5-fold. Patients with a score of 5-7 have a 3-fold increased risk and those with a score of 8 have a 2-fold increased risk[2].

In the current study, we planned to predict mortality in the patients group who could not undergo emergency endoscopy and the clinical Rockall score (pre endoscopic RS), calculated before endoscopy, was applied

In cases at high risk according to the clinical Rockall scoring, the risk of mortality was 6.022-fold greater. The ODDS value for Rockall scoring was determined as 6.022 (95% CI: 2.148-16.882). According to this, the clinical Rockall scoring system was found to be significant in predicting mortality.

In 1997, Blatchford et al published a prospective, multi-centre study of the epidemiology and mortality of upper GIS bleeding in patients in the west of Scotland[3]. Then with a prospective study in 2000, the Glasgow-Blatchford score was confirmed in 197 patients presenting with upper GIS bleeding[10]. This risk classification system does not include an endoscopic component, but the measured result shows whether there is a need for clinical intervention to control the bleeding and whether or not the patient would benefit from endoscopy. The Glasgow-Blatchford score performance has been compared with the Rockall score in the prediction of the need for intervention and has been found to have significantly better capability in this prediction. There are also studies that have found the Blatchford and Rockall scores to be equal in the prediction of mortality[2, 8,9,10]. However, unlike the previous literature, no statistically significant difference was seen in the mortality rates of the current study cases at high and very high risk according to the Blatchford score. According to Tham T.C.K et al. , they studied the clinical rocall scoring system in acute non-variceal upper gastrointestinal haemorragia and defined the pre-endoscopic rockall scoring system as useful[11].

In conclusion, the Blatchford and pre-endoscopic Rockall scoring systems were not seen to be consistent with each other and in the prediction of mortality, pre- endoscopic Rockall scoring was determined to be better (Figure 3). By accepting the high risk of mortality, monitorisation and close follow-up is recommended for cases determined as high risk according to pre-endoscopic Rockall scoring.

## Limitations

There were some limitations to this study, primarily that it was conducted in a single centre. In addition, under nighttime conditions in our hospital, emergency endoscopy is not applied. Furthermore, as our hospital is an advanced centre on this subject, patients with more comorbidities at high risk of mortality were transfered to our hospital and were included in the evaluation.

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Case Report
Eurasian Journal of Critical Care

# Why Did The Patient with A History of ADPKD Faint? The Giant Liver Cyst Explained Everything: A Case Report

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## Abstract

Syncope is a common complaint in emergency clinics, but the symptoms of syncope are quite comprehensive. In this study, we are going to present a case of a non-parasitic giant liver cyst that caused compression of the inferior vena cava with the right atrium in a 47-year-old female patient with a history of autosomal dominant polycystic kidney disease who applied to the emergency department due to syncope. In the examinations performed in the emergency department, we detected a giant liver cyst pressing on the inferior vena cava, right atrium, and ventricle of the heart, which prevents venous return. Sclerotherapy with catheterization was applied to the non-parasitic giant liver cyst and the drainage catheter was kept in the cyst cavity for one week to prevent an early recurrence.

**Key words:** Giant hepatic cyst, syncope, orthostatic hypotension, heart compression, inferior vena cava compression

## Introduction

Syncope is a sudden and brief loss of consciousness associated with a loss of postural tone following spontaneous recovery. The general pathophysiology of syncope types consists of a sudden decrease or short-term interruption of cerebral blood flow[1].

Causes of syncope range from non-serious to potentially fatal. The most common causes of syncope are cardiovascular pathologies, orthostatic hypotension and reflex also known as neural-mediated hypotension[1].

Initial evaluation, a detailed history, detailed physical examination, electrocardiogram (ECG), blood tests are helpful in identifying the underlying cause of syncope [1].

In this case, we aimed to present an autosomal dominant polycystic kidney disease (ADPKD) patient who developed syncope due to the giant cyst of the liver compressing the heart and inferior vena cava (IVC).

## Case

A 47-year-old young female patient was brought to the emergency department due to syncope when she suddenly stood up. On arrival, the patient's vital signs were: blood pressure of 95/55 mmHg, oxygen saturation of 97% on room air, respiratory rate of 20 breaths/minute, heart rate of 122 beats/minutes, temperature of 36,7 degrees Celsius, fingertip blood sugar is 96 mg/dL. There was no symptoms of fever, chest pain, shortness of breath, nausea, and vomiting. At the time of syncope, a friend of the patient who was next to her prevented her from falling to the ground.

It was reported that the patient had a history of ADPKD, undergoes routine dialysis 3 times a week and has complaints of bloating, decreased food intake due to early satiety and loss of appetite for the last month. It was stated that her last dialysis treatment was 1 day prior to fainting. ECG shows sinus tachycardia with 122 beats/minute without ST, T wave change. Her neurological examination was normal. On abdominal examination, a palpable mass was palpated in the abdomen.

In the examinations, there were no scleral icterus or significant swelling in the lower extremities. Her digital rectal examination was normal. Necessary laboratory examinations were requested. Laboratory findings were Glucose 96 mg/dL (74-106), WBC 5.16 $10^3$ / $mm^3$ (4 - 10.5), NEU 3.92 $10^3$ / $mm^3$ (1.82 - 7.42), LYM 1,4 $10^3$ / $mm^3$ (0.85-3), Blood Urea Nitrogen 111 mg / dL (8 - 20), Creatinine 6.44 mg / dL (0.81 - 1.44), Alanine aminotransferase (ALT) 6 U / L, Aspartate transaminase AST- (SGOT) 4 U / L, CRP 14 mg / L (0 - 5), potassium (K): 4.71 mmol / L (3.5-5.0), sodium (Na): 136 mmol / L (138 - 145), Troponin T: 24 ng \ L (0-14) calcium: 8.87 mg / dL (8.5-10.5), ph 7.36(7.35-7.45), PaCO2 40 mm Hg(35-45) , PaO2 90mm Hg (80-100), $HCO_3$ 20 mmol/L(22-26), Lactate 1.4 mmol/L(0.5-2)

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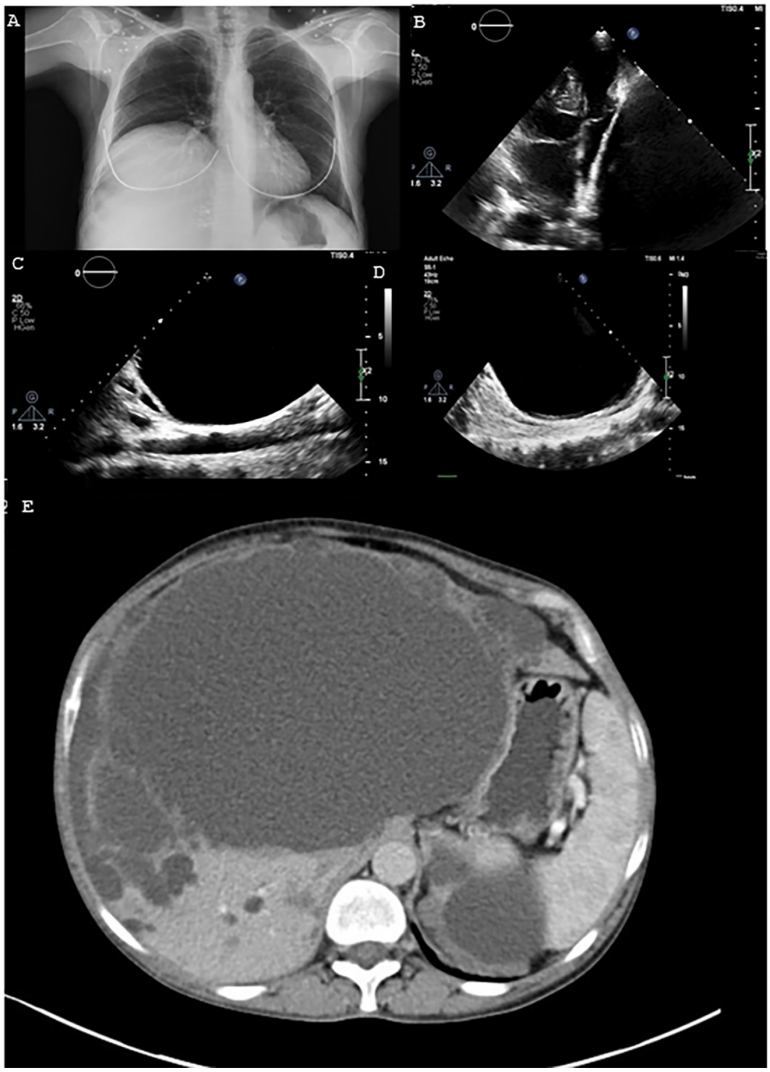


**Figure 1:** (**A**) X-ray image of lungs. (**B**) TTE imaging of compression of the RA. (**C**) Compression of the giant cyst in the liver to the inferior vena cava during inspiration. (**D**) Compression of the giant cyst in the liver to the inferior vena cava during expiration. (**E**) CT axial plane at the largest cyst diameter level: 21 x 15.5 cm.

The patient was administered a physiological saline solution. Cranial tomography and diffusion MRI was found to be normal. Elevation in the right diaphragm was detected on chest X-ray. (Figure 1: A) Bedside echocardiography was performed to investigate the cause of syncope.

In our patient with normal ejection fraction, an extracardiac mass compressing the right atrium and right ventricle was observed(Figure 1: B) Mass turned out to be a giant liver cyst and severe IVC compression (≥70%) was detected on abdominal USG. (Figure 1: C-D). Venous Doppler was found to be normal in the bilateral lower extremities. Intravenous opaque thorax and abdomen CT showed along with many small cysts in the liver, a giant liver cyst of 21x15.5 cm putting pressure on inferior vena cava, stomach, diaphragm and mild pressure on the gallbladder. The common bile duct and intrahepatic bile ducts appears normal. (Figure 1: E) There were multiple cysts in both kidneys. Pulmonary embolism and thrombus in the inferior vena cava were not observed.

No significant changes were detected in cardiac marker and ECG follow-up. The compression of the giant liver cyst was suspected as the underlying cause for syncope. The patient was hospitalized for the application of drainage of the symptomatic giant liver cyst.

## Discussion

Syncope is a common main complaint at emergency clinic admission. Causes of syncope range from non-serious to potentially fatal ones[2]. Cardiovascular pathologies, orthostatic hypotension and reflex also known as neural mediated are the most known causes of syncope [1].

In our case, a giant cyst in the liver, which was detected by ultrasonography in the emergency department, was compressing the inferior vena cava and right atrium ventricular. When the patient abruptly stood up, a giant liver cyst that compressing the inferior vena cava reduced venous return hence syncope occured due to orthostatic hypotension. No pathological findings explaining the clinic were detected in the laboratory examination. Gastrointestinal bleeding was

not considered in the foreground with the presence of normal stool contamination in digital rectal examination. It was thought that a possible cardiac dysrhythmia that could cause syncope would be unlikely due to obviously appearing giant hepatic cyst that prevented venous return. In a case report similar to our case, syncope developed due to the compression of the giant cyst in the liver on the heart and inferior vena cava [3].

A case of Polycystic Kidney Disease (PKD) with right-sided heart failure due to liver cysts pressing on the right atrium have been described in the related literature [4]. Our patient had both right atrial and right ventricular compression, but there was no evidence of right heart failure.

Most simple cysts in the liver are usually detected incidentally on imaging because of their asymptomatic behavior. The most commonly encountered symptom in this patient group is abdominal pain [5]. Interestingly, our patient did not have severely disturbing abdominal pain. She stated that she felt the bulk in her abdomen, but she did not seek treatment at the hospital before because she did not have any disturbing pain.

Large cysts in the liver show obvious symptoms such as abdominal bloating, fullness, early satiety, nausea, and vomiting. The most common complications of liver cysts are rupture, infection, obstructive jaundice, cyst bleeding, portal vein occlusion with splenic varices, and inferior vena cava thrombosis [6].

The reason for the patient's early satiety and decreased oral intake is due to the compression of the stomach by the giant cyst detected in the liver. No thrombus was detected in the inferior vena cava and pulmonary artery in Contrast CT. There was no evidence of obstructive jaundice infection. One of the case-control study of the patients with APDKD found that the prevalence of IVC compression by kidney or liver cysts was dramatically higher in women older than 40 years and in women [6].

This is due to the fact that vena cava compression occurs in women who are more likely to have more and larger liver cysts than men, possibly due to an estrogen-related mechanism [7]. The fact that our patient was over 40 years old, and female supports this hypothesis.

In addition, in this study, it was found that some of the cases with IVC compression worsen progressively. In addition, no regression was detected in IVC compression in any of them. Therefore, symptomatic patients require intervention. Percutaneous aspiration or surgical intervention is required [8].

For symptomatic non-parasitic liver cysts, the recommended treatment modalities are open deroofing and percutaneous sclerotherapy, as simple drainage often results in recurrence [9]. In our case, sclerotherapy was performed with catheterization and the drainage catheter was kept in the cyst cavity for a week to prevent an early recurrence.

In conclusion, IVC compression by hepatic cysts formation in APDKD patients is an important vascular complication. This should be kept in mind when evaluating APDKD patients in the emergency department.

## Conclusion

Due to the irregular follow-ups, the size of the cysts formed in the kidney and other organs of our patient with APDKD was not followed up, that's why a liver cyst of that size wasn't diagnosed earlier. In patients diagnosed with APDKD, ultrasound should be performed at regular intervals to monitor the size of the possible cysts. When evaluating APDKD patients in the emergency department, we suggest that patients should be evaluated quickly with bedside ultrasound for pathologies caused by cysts developing in the kidneys and other organs.

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Case Report
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# Emphysematous Gastritis – A Rare Cause of Porto-mesenteric Venous Gas

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## Abstract

Porto-mesenteric venous gas is an ominous radiologic sign. It is associated with severe intra-abdominal diseases that often require surgical management. In this case report, we present a 66-year old male who was brought to our Emergency Department for multiple episodes of vomiting and non-bloody diarrhea. Computed tomography of the abdomen showed porto-mesenteric venous gas due to emphysematous gastritis. He subsequently developed multi-organ failure from Klebsiella pneumoniae septicemia but made a full recovery after a prolonged course of supportive therapy and systemic antibiotics in the Intensive Care Unit. This case report highlights why it is clinically important and relevant for emergency physicians to be aware of this rare clinical condition associated with high mortality rate.

**Key words:** Abdominal Pain, Computed Tomography, Emphysematous Gastritis

## Introduction

Porto-mesenteric venous gas is an ominous radiologic sign – it is often associated with severe intra-abdominal diseases such as bowel ischemia or mesenteric vascular accident[1]. This accumulation of gas in the porto-mesenteric system can be attributable to the presence of gas-forming organisms in the porto-mesenteric system, or the circulation of gas produced by gas-forming organisms in the bowel wall or intra-abdominal abscess to the porto-mesenteric system[2]. The diagnosis of porto-mesenteric venous gas can be made by x-ray, ultrasound, colour Doppler flow study or computed tomography (CT) scan. With the ubiquitous use of CT scan in the emergency departments (EDs), the presence of porto-mesenteric venous gas is being detected earlier and with higher sensitivity[3]. Here, we present a case report on porto-mesenteric venous gas due to emphysematous gastritis.

## Case Report

A 66-year-old male with a past medical history of diabetes mellitus and dyslipidemia presented with a 3-day history of diffuse colicky abdominal pain associated with multiple episodes of vomiting and non-bloody diarrhea. He otherwise had no fever nor any significant contact or travel history. He was afebrile, in sinus tachycardia with a heart rate of 162 beats per minute and hypotensive with a blood pressure of 88/63mmHg. Physical examination revealed dry mucous membranes, a soft but distended abdomen without peritonism, and an empty rectum on digital rectal examination.

Initial laboratory investigations revealed a raised white blood cell count of 33.2 x 109/L, lactic acidosis with a serum lactate of 12.3mmol/L, serum pH of 7.33 and serum bicarbonate of 13.3mmol/L and acute kidney injury with a serum creatinine of 275mcmol/L from a previously normal baseline. A CT scan of the abdomen and pelvis revealed diffuse gas within the porto-mesenteric venous system including the intra-hepatic portal venous branches of the right hepatic lobe, splenic vein and mesenteric venous tributaries, as well as intramural gas in the posterior gastric wall, (Figures 1 to 3). The small bowel loops were diffusely dilated in keeping with ileus without obvious mechanical obstruction. There was otherwise no obvious pneumoperitoneum or free intra-abdominal fluid, and assessment of mesenteric ischemia was limited by the non-contrasted CT scan performed in view of the significant risk of contrast-induced nephropathy.

With a clinical suspicion of acute mesenteric ischemia, the patient was counselled for and underwent an exploratory laparotomy. Surgical exploration revealed healthy and viable stomach, small bowel and colon down to the rectum, without any evidence of perforation or free peritoneal fluid. With the exclusion of acute mesenteric ischemia, a clinical diagnosis of septic shock secondary to emphysematous gastritis was made. The abdomen was closed primarily, and the patient was sent to the intensive care unit for further

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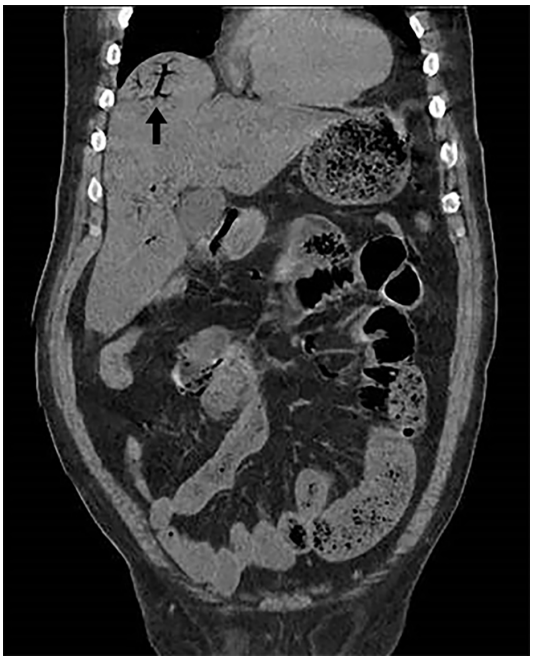

**Figure 1:** Computed tomography scan of the abdomen and pelvis without intravenous contrast. Portal venous gas (arrow) within the right lobe of the liver is shown in coronal view.

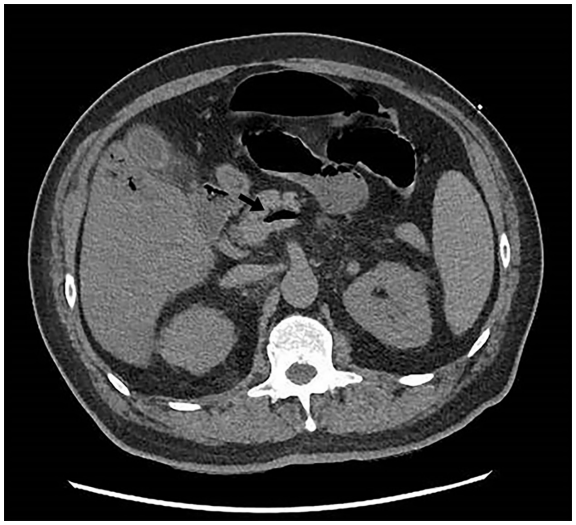

**Figure 2:** Computed tomography scan of the abdomen and pelvis without intravenous contrast. Gas (arrow) within the splenic vein is shown in axial view.

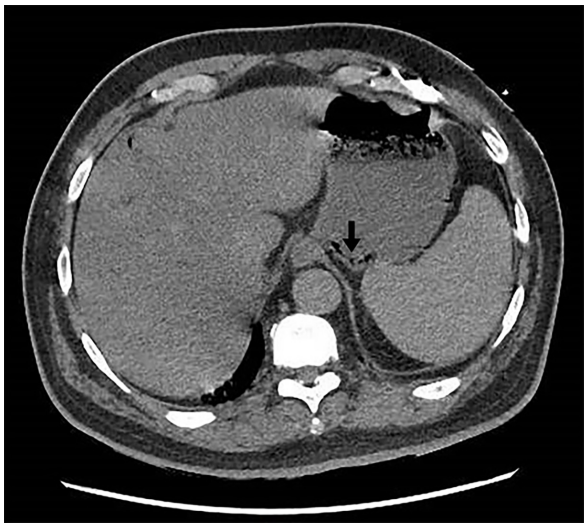

**Figure 3:** Computed tomography scan of the abdomen and pelvis without intravenous contrast. Gas (arrow) within the posterior gastric wall is shown in axial view.

management. After a stormy inpatient stay complicated by multi-organ failure from Klebsiella pneumoniae septicemia, he made a full recovery after a prolonged course of supportive therapy and systemic antibiotics.

Consent was obtained from the patient for this case report.

## Discussion

Emphysematous gastritis is caused by gas forming organisms invading the gastric mucosa with resultant necrotizing infection of the gastric wall[4-6]. Common causative organisms include Streptococcus species, gram-negative bacilli such as Escherichia coli, Enterobacter species and Klebsiella species, as well as anaerobes such as Clostridium perfringens[4]. These organisms can invade the gastric mucosa by either local infection or hematogenous spread. The gastric wall is usually resistant to infection as its rich blood supply and acidic pH make it an efficient barrier. However, predisposing factors including diabetes mellitus, use of alcohol and non-steroidal anti-inflammatory drug, as well as toxic ingestion to corrosive agents can threaten the integrity of the gastric wall, thus making a patient susceptible to this rare but lethal condition[4,5]. Necrotic gastric tissue may be found in vomitus or aspirate from nasogastric tube and is pathognomic[5].

The CT images of this case report demonstrated the florid findings of porto-mesenteric venous gas and intramural gas within the gastric wall effectively. In the clinical context of this case report, the two key differential diagnoses to consider are acute mesenteric ischemia and emphysematous gastritis. Differentiating the two may be challenging clinically, but a potential diagnostic clue supporting a diagnosis of emphysematous gastritis include the absence of large vessel occlusive disease on cross sectional imaging. While surgery is often mandatory in the treatment of acute mesenteric ischemia, emphysematous gastritis can be treated medically with broad spectrum intravenous antibiotics, proton pump inhibitors, as well as supportive management for hemodynamic stabilization and nutritional support[5,6]. However, a high index of suspicion is paramount as treatment must be instituted promptly in order to reduce the high mortality rate of up to 60% associated with the condition[7]. Surgery is required when there is clinical deterioration, failure of medical therapy, gastric perforation and stricture formation. Surgery is also required when the case is indeterminate such as ours, for the definitive exclusion of acute mesenteric ischemia.

The radiologic finding of porto-mesenteric venous gas has conventionally been associated with severe intra-abdominal diseases often necessitating surgical management. However, emergency physicians must be aware that with CT scan being available as a ubiquitous imaging tool, the presence of porto-mesenteric venous gas may not by itself be an indication for surgery or adverse outcome. Accurate history and thorough physical examination remain crucial so that clinical symptoms and signs can be correlated with radiological findings. Ultimately, the treatment and prognosis of the patient must be based on the underlying disease pathology suspected on clinical grounds.

## Conclusion

Emphysematous gastritis is associated with significant morbidity and mortality for the patient, necessity prompt diagnosis and management in the ED.

## Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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Case Report
Eurasian Journal of Critical Care

# A Fatal Side Effect of Piperacillin/Tazobactam Use: A Case Report

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## Abstract

Drug-induced QT prolongation with T wave inversion is a complex regulatory and clinical problem due to the rarity of this potentially fatal adverse incident. A 68-year-old female patient was receiving piperacillin/tazobactam therapy for a complicated urinary tract infection. She has had normal ECG findings before the antibacterial therapy. After the treatment, the patient worsens due to long QT which is predisposed to torsades de pointes. As a result of the researches, it was understood that the cause of long QT was piperacillin/tazobactam. We aimed to present a rare case in which we detected drug-induced QTc prolongation with piperacillin/tazobactam in clinical practice.

**Key words:** Torsades de Pointes, drug-induced long QT syndrome, piperacillin/tazobactam, T-wave inversion, urinary tract infection

## Introduction

The QT interval seen on the electrocardiogram (ECG) reflects the electrical depolarization and repolarization of the ventricles. The normal range of the rate-corrected QT (QTc) intervals was determined as (<0.47s) and (<0.45s) in females and males, respectively[1]. The QT interval prolongation is a clinically and genetically heterogeneous syndrome characterized by syncope and sudden death due to a tendency to ventricular fibrillation, torsades de pointes and ventricular arrhythmia[2]. QT interval may be prolonged by hypokalemia, hypomagnesemia, hypocalcemia, myocardial ischemia, post-cardiac arrest, increased intracranial pressure, congenital long QT syndrome and drugs. It has been identified that many drugs such as antihistamines, antibiotics, antidepressants and prokinetics may cause drug-induced prolonged QT syndrome (diLQTS)[3]. The mechanism for the drug that prolongs the QT time is due to the inhibition of the one encoded by KCNH2. HERG (the human Ether-à-go-go-Related Gene) prolongs QT interval by inhibiting the potassium channel, causing delayed action potential[4]. We present a rare case report by using piperacillin-tazobactam-induced long QT syndrome.

## Case Report

A 68-year-old female patient with a history of hypertension was admitted to the emergency department with the complaint of fainting and feeling like her heart would stop.

ECG was notable for QT prolongations in multiple leads and deep symmetrical T wave inversion(Figure1) (QTc, Bazett correction = 542 ms). Patient was admitted to the critical care area of the emergency department clinic with the pre-diagnosis of the acute coronary syndrome and cerebrovascular event by emergency medicine specialists.

On arrival, the patient's vital signs were: blood pressure of 110/ 70 mmHg, heart rate of 65 beats per minute, respiratory rate of 18 breaths per minute, temperature of 36,5 degrees Celsius, and an oxygen saturation of 96% on room air. Blood glucose measurement from the fingertip is 100 mg/dl. No intracranial pathology was detected in cranial CT and MRI. Laboratory findings were WBC 11.9 103 / mm3 (4 - 10.5), NEU 8.7 103 / mm3 (1.82 - 7.42), LYM 2.8 103 / mm3 (0.85-3), Blood Urea Nitrogen 25 mg / dL (8 - 20), Creatinine 0.96 mg / dL (0.81 - 1.44), Alanine aminotransferase (ALT) 40 U / L, Aspartate transaminase AST- (SGOT) 52 U / L, CRP 20.8 mg / L (0 - 5), potassium (K): 3.6 mmol / L (3.5-5.0), sodium (Na): 136 mmol / L (138 - 145), Troponin T: 22 ng \ L (0-14) calcium: 8.6 mg / dL (8.5-10.5), magnesium 1.91 mmol / L (1.8-2.6).Transthoracic echocardiography performed in the emergency department revealed degenerative mitral and aortic valves and mild left ventricular hypertrophy (Figure 2). She was hospitalized to the coronary intensive care unit because at her ECG, a prolonged QT was also detected. She was under home treatment with valsartan/hydrochlorothiazide and acetylsalicylic acid. One hour after hospitalization in the coronary intensive care unit, CPR was initiated and defibrillation was performed rapidly

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following the transition of the patient into an unconscious state and development of torsades de pointes, known as a fatal dysrhythmia, seen in the monitor. 2 gr Magnesium IV was administered. Coronary angiography was performed after rhythm recovery. Coronary angiography revealed uncritical plaques in the left anterior descending coronary artery (LAD) and right coronary artery (RCA). There was no detected abnormality in the laboratory results. There were no substantial reasons explaining prolonged QT. When the hospital registry system was checked, it was seen that the patient was discharged from our hospital about 15 hours ago. When the summary of discharge from the hospital was reviewed, it turned out that she was treated with piperacillin/tazobactam due to a complicated urinary tract infection due to E Coli producing ESBL in urine culture. Previous ECG taken before piperacillin/tazobactam treatment, shows no QT prolongation and T wave inversion(figure 3). It was found that the prolonged QT finding and deep T wave inversion of the patient, who was followed up in the coronary intensive care unit, resolved spontaneously. After ruling out other causes that could cause prolonged QT, it was thought that the cause of prolonged QT was likely to have resulted from piperacillin/tazobactam administration.

## Discussion

Long QT syndrome (LQTS) is associated with fatal arrhythmias such as torsades de pointes and ventricular fibrillation[2]. As a matter of fact, torsades de pointes, which is a fatal rhythm, developed in our patient. The rhythm improved with fast and effective intervention in coronary intensive care. Electrolyte disorders such as hypokalemia, hypomagnesemia, and hypocalcemia that could cause long QT in our patient were ruled out with normal laboratory values. Intracranial pathologies were ruled out with cranial imaging. Since noncritical plaques and strictures were detected in coronary angiography, acute coronary syndrome that could cause long QT was also ruled out. Abnormal QT/QTc prolongation can be categorized into two groups as the congenital and the acquired variant the latter of which can generally be related with a certain group of drugs prolonging the QT/QTc interval. Arizona Center for Education and Research on Therapeutics (CERT) have issued a specific list of drugs with suspected TdP liability. Analyzing data from the United States Food and Drug Administration (USFDA) Adverse Event Reporting System, Poluzzi et al. reported additional drugs that can cause QT prolongation and TdP, which includes piperacillin/tazobactam and metronidazole[5]. In a study, using data between 2004 and 2008, conducted by the US Food and Drug Administration (FDA) Adverse Event Reporting System, it was found that overall 374 reports of diLQTS/TdP had been associated with antimicrobial drugs, more than half of which (62%) were detected to have links to antibacterial agents mostly to macrolides and fluoroquinolones[6]. 3.581 people who had adverse effects when taking piperacillin/tazobactam were reported between 1997 and 2018 from FDA reports on Feb, 25, 2018. Among them, total of four people, two in 2011, one in 2012, and one in 2014 (0.11%) had long QT syndrome. Our patient who developed long qt due to piperacillin/tazobactam intake is the fifth case report in the literature in this sense. Accumulating publications mostly in the form of case reports and case series pertaining to affected patients indicate that diLQTS/TdP with T wave inversion constitutes a problem cannot be unnoticed. Since it can lead to long QT and cause torsades de pointes, a fatal rhythm, piperacillin/tazobactam used in the treatment of patients with severe lower respiratory tract infections involving hospital-acquired pneumonia and ventilator-associated pneumonia, complicated urinary tract infections (including pyelonephritis), complicated intraabdominal infections, neutropenic fever, high-risk cancer patients, the ones with bacteremia associated, or likely to be associated with various infections as complicated skin and deep tissue infections (mainly in the form of diabetic foot infections)[7], are recommended to be administered with cardiac monitoring.

## Conclusion

The real number of cases pertaining to drug-induced prolonged QTc with piperacillin/tazobactam in clinical practice is not exactly known. The present case clearly emphasizes the significance of reconsidering and even avoiding the administration of QT-prolonging drugs in hospitalized patients, due to the fact that hospitalized patients often have the potential to exhibit a proarrhythmic response resulting from various risk factors. Early recognition and appropriate management may lead to normalization of the ECG changes and prevent hemodynamic deterioration or death as in our case.

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