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|---|---|---|---|---|---|
| Original Article | 5000 (Structured) | 200 | 50 | 6 | 7 or total of 15 images |
| Review Article | 5000 | 200 | 50 | 6 | 10 or total of 20 images |
| Case Report | 1500 | 200 | 10 | No tables | 10 or total of 20 images |
| Letter to the Editor | 500 | N/A | 5 | No tables | No media |
| Scientific letter | 900 | N/A | 10 | No tables | 2 or total of 4 images |
| Clinical Imaging/ Visual Diagnosis | 400 | N/A | 5 | No tables | 3 or total of 6 images |
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| Publication ethics | 900 | N/A | 10 | No tables | No media |

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# CONTENTS

EURASIAN JOURNAL OF EMERGENCY MEDICINE


# "Emergency Care in Germany being re-assessed"

## Hybrid Medical Care Model Seen As Potential Answer


Germany must seek new concepts for provision of emergency care which meet the conflicting pressures between performance quality and performance efficiency.

Emergency medical care in Germany is currently mainly provided by hospital emergency departments and by emergency medical practices established by the association of physicians providing care inside the terms of the standard and compulsory health insurance scheme. The pre-hospital emergency doctor service mainly stabilises patients and transports them to other places for treatment.

Efforts to improve efficiency in hospital emergency departments are facing heavy resistance from the societies representing non-emergency medical specialties. Calls for a medical specialty for emergency medicine have been refused for no major reason other than claims the status quo is satisfactory.

The main reason for the opposition by other societies is difficult for them to say publicly: They do not wish the balance of power held by the existing medical specialities in the federal medical council to be disrupted by a new specialty.

Instead a supra specialty in emergency medicine was offered and accepted by the German Association for Emergency Medicine. The authors fear that is a delaying tactic by the other societies and the record in other European countries shows that this course will remove the subject of the emergency medicine physician from the agenda in Germany perhaps for 15 to 20 years.

In the meantime, rising numbers of emergency patients are being registered in Germany. The number of hospitals is being reduced, especially in rural areas and general medical practices are increasingly refusing to provide emergency care outside normal working hours or at weekends.

The emergency services set up by the association of general physicians working in the standard medical insurance sector has been criticised as unsatisfactory by politicians and by patients. There is criticism about serious lack of capacity at weekends and non convenience times which has led to shortcomings in care provision.

With attempts to improve emergency department efficiency blocked and the services provided by the association of physicians inadequate, more attention is now needed in Germany to deal with the serious problems in emergency outpatient care by using polyclinic service centres.

Polyclinic service centres could provide a major part of the answer through a hybrid character. This would display the characteristics of a 24 hour/7 day a week opening convenience clinic which would deal professionally with the "non urgent" emergency cases and so provide a major service potential. Polyclinics are present in many small towns and in rural areas but simply close at the weekend or in the evening. Their latent capacity could be used in emergency services.

Polyclinics can provide diagnostics and treatment which was previously only possible in hospitals. In the event that a patient has a life-threatening illness, polyclinics can act as a dispatcher in a hub and spoke model, transferring patients to other hospitals or clinics with capacity to treat them.

The evident need for a 24 hour a day/7 day a week comfort care system will overreach the service provided by the association of general practices, whose service will increasingly look obsolete. Polyclinics can become services offering treatment to discerning customers demanding extensive access to the best possible medical care.

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# Diagnostic Value of Signal Peptide, CUB (Complement C1r/C1s, Uegf, and Bmp1), EGF (Epidermal Growth Factor)-Like Domain-Containing Protein 1 (SCUBE1) and Chemerin in Experimental Testicular Torsion

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## Abstract

**Aim:** The purpose of this experimental study was to investigate the potential diagnostic value of the platelet activation marker SCUBE1 [signal peptide, CUB (complement C1r/C1s, Uegf, and Bmp1), and EGF (epidermal growth factor)-like domain-containing protein 1] and the adipocytokine chemerin in a prepubertal rat model of testicular torsion (TT).

**Materials and Methods:** Twenty-eight male rats were used for this study. They were randomly assigned into one of the four groups, each containing seven rats. No additional procedure other than a sham operation was performed on the control group (group IV). The other subjects comprised the torsion ischemia groups (groups I, II, and III). Blood specimens were collected after 30 min (group I), 2 h (group II), or 4 h (group III) using the intracardiac method. For group IV, which was the sham operation group, blood specimens were collected after 4 h, and testis tissue specimens were extracted by orchiectomy for histopathological examination.

**Results:** No statistically significant change was determined in SCUBE1 levels of rats exposed to torsion. Also, no significant difference was observed between SCUBE1 levels of rats exposed to torsion and those of the control group. Statistically significant change was determined in chemerin levels during observation in rats exposed to torsion. This change was statistically significant between groups I and III. There was no statistically significant difference between chemerin levels of rats exposed to torsion (groups I, II, and III) and those of the control group (group IV).

**Conclusion:** We observed no statistically significant differences when plasma SCUBE1 and chemerin levels of rats subjected to TT were compared with a control group in this study.

**Keywords:** Chemerin, experimental study, rat model, SCUBE1, testicular torsion

## Introduction

Testicular torsion (TT) is a condition more commonly seen in children and it requires emergency surgery (1). Torsion of the spermatic cord occurs, and the spermatic blood vessels are obstructed. If detorsion is not performed within a suitable time frame, the testis undergoes necrosis (2). If the duration of ischemia exceeds 6 h, permanent injury occurs in the germinal epithelium. Early identification of the effect of reperfusion in the germinal epithelium and surgical intervention are therefore highly important (3). Since there is no additional medical treatment to protect the testis against ischemia-reperfusion injury apart from surgical repairing, there are no sufficiently sensitive standard diagnostic or prognostic markers. There is therefore a need for novel, sensitive diagnostic or prognostic biochemical markers (4).

SCUBE1 [signal peptide, CUB (complement C1r/C1s, Uegf, and Bmp1), and EGF (epidermal growth factor)-like domain-containing protein 1] is a newly described cell surface protein (5) and is thought to be a novel platelet endothelial adhesion molecule. SCUBE1 accumulation has been determined immunohistochemically in the subendothelial matrix of advanced atherosclerotic lesions in humans. It is stored in platelet granules and is released from thrombin-activated platelet granules, where it enters the thrombus (6). Chemerin is one of the

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several recently discovered adipokines released from adipose tissue. It is released in an inactive state, prochemerin, from adipose and other tissues. It is converted into chemerin by plasmin, factor XIIa, and C1s belonging to the coagulation and fibrinolytic mechanism, neutrophil elastase and cathepsin G released from activated neutrophil granules and serine proteases released from mast cells by undergoing cleavage from the C-terminal end. Chemerin is a ligand for the G-protein–coupled chemokine-like receptor-1 (CMKLR1). CMKLR1 is primarily found in immune system cells such as dendritic cells, activated neutrophils, and macrophages (7, 8). Chemerin has a potential role in the immune response by performing a chemotactic function for cells releasing antigens in inflammation or tissue injury (7, 9).

Platelet and neutrophil activation occurs as a result of vascular endothelium injury following ischemia in TT (10). The limited studies in the literature have investigated the relation between platelet activation and testicular ischemia and have revealed that this may play an important role in the pathology of tissue injury. One experimental study reported that measurement of plasma SCUBE1 levels may be of diagnostic, therapeutic, or prognostic value but further studies are needed to confirm this (11). Our scan of the literature revealed no studies investigating the conversion into chemerin of inactive prochemerin and substances released from activated neutrophil granules and the diagnostic significance of serum levels thereof in TT. The purpose of this experimental study was to investigate the potential diagnostic value of the platelet activation marker SCUBE1 and the adipocytokine chemerin in a prepubertal rat model of TT.

## Materials and Methods

### Study design and selection of subjects

This experimental study was performed following receipt of ethical committee approval (No. 2015/67). Twenty-eight prepubertal male Wistar--Hannover rats with a mean age of 30 days and weighing 75–125 grams were used. The experimental animals were kept at a temperature of 22°C±1°C, in a 12-hour light:12-hour dark cycle, at a humidity level of 50%-60%. Rats were given standard pellet chow and city drinking water until the day of the experiment. Rats were fasted for 12 hours preoperatively.

### Study protocol

Twenty-eight male rats were used for this study. They were randomly assigned into one of the four groups, each containing seven rats.

Group I: (n=7); blood specimens taken 30 min after induction of torsion ischemia.

Group II: (n=7); blood specimens taken 2 h after induction of torsion ischemia.

Group III: (n=7); blood specimens taken 4 h after induction of torsion ischemia.

Group IV: (n=7); control group, a sham operation group.

General anesthesia was induced before surgery with peritoneal injection of 10 mg/kg xylazine and 70 mg/kg ketamine hydrochloride. The skin of the scrotum was cleaned with 10% povidone iodine solution. A 2-cm vertical, cutaneous and subcutaneous, midline incision was made in the scrotum. The left testes in the scrotal space, together with the tunica vaginalis and spermatic cord, were separated from the gubernaculum with blunt dissection and removed/exposed. No additional procedure other than a sham operation was performed on the control group (group IV). The other subjects comprised the torsion ischemia groups (groups I, II, and III). In these groups, an experimental extravaginal model of TT was established by rotating the left testes and their cord elements 720 degrees in a clockwise direction. The testis subjected to torsion was attached to the inner surface of the scrotum in two locations using 4/0 propylene sutures. Blood specimens were collected after 30 min (group I), 2 h (group II), or 4 h (group III) using the intracardiac method. Left testis tissues exposed to torsion were extracted with orchiectomy from all groups for histopathological evaluation. For group IV, the sham operation group, blood specimens were collected after 4 h, and testis tissue specimens were extracted by orchiectomy for histopathological examination. The specimens obtained were frozen and stored.

## Laboratory analysis

### SCUBE1 and chemerin measurement

An ELISA kit (Catalog No. CSB-E16229r; Cusabio Biotech Co., Wuhan, Hubei, People's Republic of China) was used to determine SCUBE1 levels, following the manufacturer's instructions. Specimen absorbances were determined on a Biotek ELX800 (Biotek, Winooski, VT) microplate reader at a wavelength of 450 nm. The results were expressed in ng/mL. The minimum detectable dose was 0.625 ng/mL.

An ELISA kit (Catalog No.CSB-EL019324RA; Cusabio Biotech Co.) was used to determine chemerin levels, following the manufacturer's instructions. Specimen absorbances were determined on a Biotek ELX800 (Biotek) microplate reader at a wavelength of 450 nm. The results were expressed in ng/mL. The minimum detectable dose was 0.9 g/mL.

### Histological analysis and staining

Testis tissue specimens were fixed in Bouin's solution for histopathological examination. Following routine procedures, tissues were fixed in paraffin blocks. Four-micrometer-thick sections were taken. Following staining with hematoxylin and eosin (HE), these were examined under light microscope in line with the classification described by Cosentino et al. (12).

### Statistical analysis

Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 15.0 for Windows software was used for statistical analysis. Since parametric test conditions could not be established, comparisons of more than two independent groups were performed using the Kruskal–Wallis test. Subgroup analyzes were performed with the Mann–Whitney U test and interpreted with Bonferroni correction. Dependent group analyzes were performed with the Wilcoxon test and interpreted with Bonferroni correction. Statistical alpha significance was set at $p<0.05$.

## Results

### Biochemical parameters

Time-dependent biochemical parameter results by groups are shown in Table 1. No statistically significant change was determined in SCUBE1 levels of rats exposed to torsion. Also, no significant difference was observed between SCUBE1 levels of rats exposed to torsion and those of the control group ($p=0.422$).

**Table 1.** Time-dependent changes in SCUBE1 and chemerin

| | Group I | Group II | Group III | Group IV | | |
|---|---|---|---|---|---|---|
| | Median (95% CI) | Median (95% CI) | Median (95% CI) | Median (95% CI) | p* | |
| Rat SCUBE (ng/mL) | 19.1 (4.4 –54.4) | 22.0 (-5.5–79.7) | 13.6 (3.9–39.6) | 20.6 (-10.4–90.5) | 0.422 | |
| Rat Chemerin (ng/L) | 23.6 (16.2–57.9) | 19.1 (17.2–21.5) | 15.9 (14.2–17.3) | 16.2 (12.8–24.9) | 0.004 | |
| | **Group I vs. II** | **Group I vs. III** | **Group I vs. IV** | **Group II vs. III** | **Group II vs. IV** | **Group III vs. IV** |
| p | 0.048 | 0.003 | 0.032 | 0.011 | 0.199 | 0.605 |

Abbreviation: CI, confidence interval.
*Kruskal–Wallis test.
**Mann–Whitney U test: Bonferroni correction p<0.0083

Statistically significant change was determined in chemerin levels during observation in rats exposed to torsion (p=0.004). This change was statistically significant between groups I and III (p=0.003). There was no statistically significant difference between chemerin levels of rats exposed to torsion (groups I, II, and III) and those of the control group (group IV) (p=0.605).

Time-dependent torsion and control group SCUBE1 results are shown in Figure 1 and chemerin results in Figure 2.

**Histopathological examination**

Testis tissues from both the torsion and control groups were examined. Analysis of group I tissue of the testisrevealed minimal interstitial hemorrhage and changes in germ cell arrangement (grade 2) (Figure 3). Pronounced hemorrhage and irregular, occasionally necrotic and necrobiotic germ cells were observed in group II testis tissue (grades 2 and 3) (Figure 4). Irregular germ cells, cells shedding into the lumen, and occasional coagulation necrosis were observed in testis tissue from group III (grades 3 and 4) (Figure 5). Histopathology of testis tissues from the control group (group IV) was grade 1, and these findings were compatible with normal testis tissue both macro- and microscopically (Figure 6).

A comparison of histopathological grades of group testes subjected to torsion is given in Table 2. A statistically significant difference was observed between grades in the TT groups (p<0.001). This difference was significant between all groups except for between groups I and II.

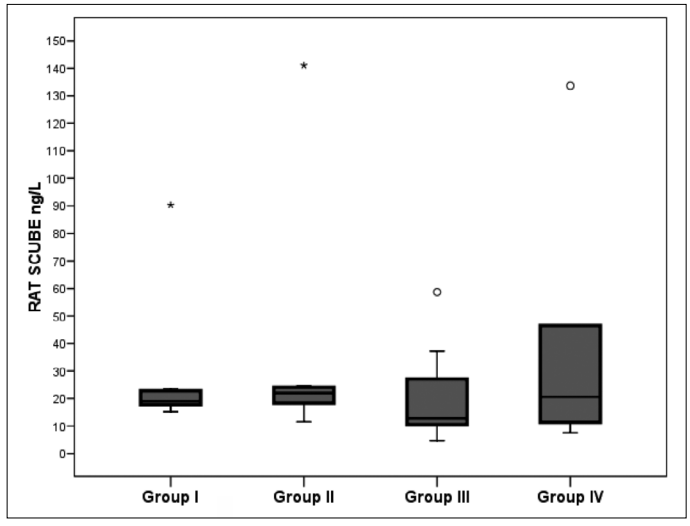


**Figure 1.** Time-dependent SCUBE1 levels in the torsion (groups I, II and III) and control group (Group IV)

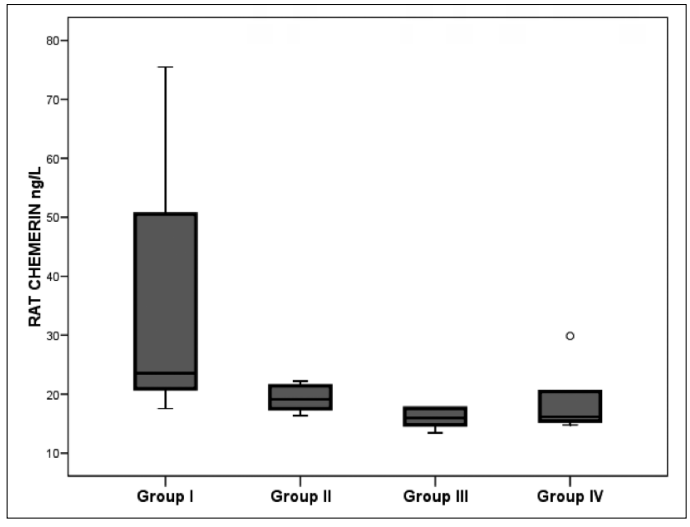


**Figure 2.** Time-dependent chemerin levels in the torsion (groups I, II and III) and control group (Group IV).

## Discussion

No statistically significant change was determined in plasma SCUBE1 levels of rats subjected to torsion at 30 min and 2 or 4 h. At the same time, no significant difference was determined in SCUBE1 levels of rats subjected to torsion compared to control group levels. No significant correlation was determined between SCUBE1 levels in TT and histopathological scoring.

SCUBE1 is a novel potential marker of platelet activation (13). This cell surface protein is largely stored in the alpha granules of the platelets. Significant amounts of SCUBE1 are secreted with platelet stimulation (14). Dai et al. (6) reported a significant increase in plasma SCUBE1 concentration acute ischemic stroke (AIS) and acute coronary syndrome (ACS), in which platelet activation is involved, and an important increase in coronary artery disease. In an experimental study, Turkmen et al. observed a sudden increase in SCUBE1 levels 2 h after acute mesenteric ischemia (AMI) and a pronounced increased in SCUBE1 levels 6 h after AMI (15).

In one study investigating the role of platelet activator factor (PAF) in testicular ischemia, the PAF antagonist CV-6209 was used before torsion; significantly, less ischemic injury was observed compared to the untreated group (16). In another study, Orhan et al. (3) used the PAF antagonist EGB-761 *Gingko biloba* after torsion and re-

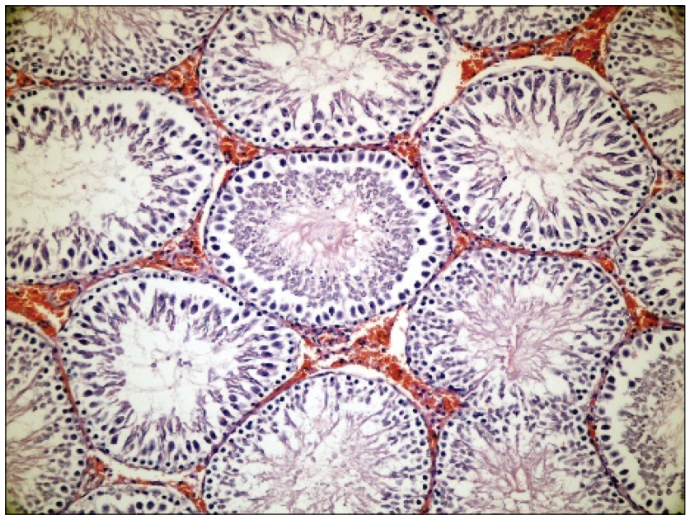

**Figure 3.** Minimal interstitial hemorrhage and changes in germ cell arrangement in the 30-min torsion group (Grade 2) (H&E X200).

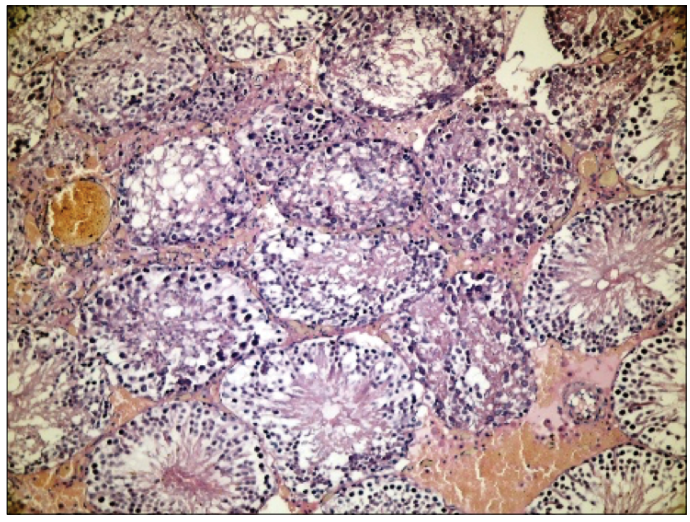

**Figure 5.** Irregular germ cells, cells shedding into the lumen and occasional coagulation necrosis in the 4-h torsion group (Grade 3 – 4) (H&E X200)

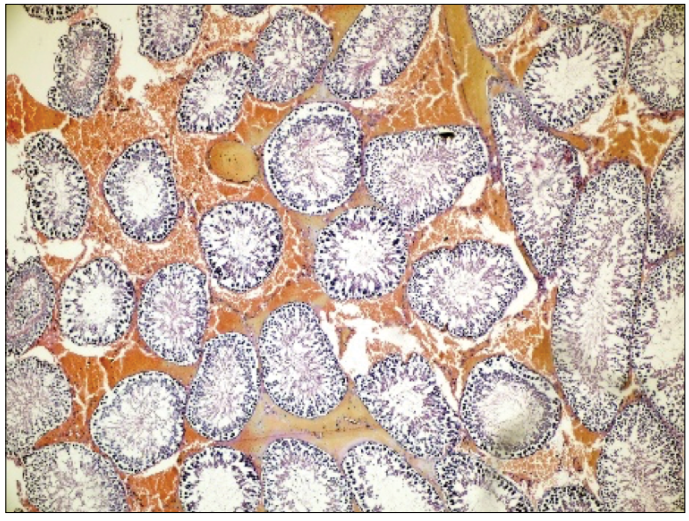

**Figure 4.** Pronounced hemorrhage and irregular, occasionally necrotic and necrobiotic germ cells in the 2-h torsion group (Grade 2 – 3). (H&E X100).

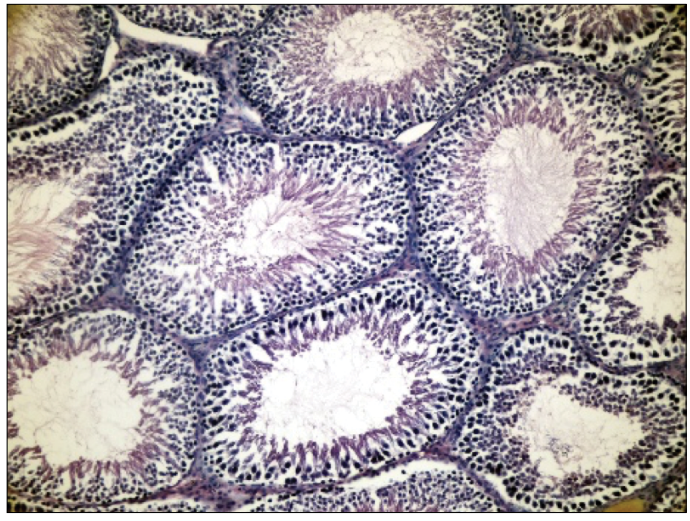

**Figure 6.** Testis tissue with a normal appearance in the control group (Grade 1) (H&E X 200).

**Table 2.** Comparison of the histopathological grades of the groups

| | | **Group I** | **Group II** | **Group III** | **Group IV** | **p*** |
|---|---|---|---|---|---|---|
| Torsion ever | Mean±SD | 2.00±0.58 | 2.29±0.49 | 3.14±0.38 | 1.00±0.00 | <0.001 |
| | Median | 2 | 2 | 3 | 1 | |
| | IQR | 2-2 | 2-3 | 3-3 | 1-1 | |
| | **Group I vs. II** | **Group I vs. III** | **Group I vs. IV** | **Group II vs. III** | **Group II vs. IV** | **Group III vs. IV** |
| p | 0.334 | 0.003 | 0.002 | 0.007 | 0.001 | <0.001 |

*Wilcoxon test and Kruskal–Wallis test.
**Mann–Whitney U test: Bonferroni correction p<0.0083. IQR: interquartile range; SD: standard deviation

ported a significant decrease in ischemic injury induced by torsion in the contralateral testis. PAF is a phospholipid mediator with powerful biological effects. It activates a broad cell group including monocytes, mast cells, and polymorphonuclear leukocytes, and particularly platelets (17). No statistically significant change was determined in the SCUBE1 levels of the torsion group in our study. No significant difference was determined between torsion groups' SCUBE1 levels and those of the control group. In an experimental study of adult rats,

Türedi et al. (11) compared plasma SCUBE1 levels in groups consisting of six rats and exposed to TT at 2 h and 4 h with control group levels at 2 and 4 h. A significant elevation in SCUBE1 levels was determined 4 h after testicular ischemia. In our study, we elected to use prepubertal rats rather than adults, as TT is more common in very young males. We measured plasma SCUBE1 levels in groups containing seven prepubertal rats each exposed to TT at 30 min, 2 h, and 4 h and levels in the control group at 4 h. No significant change was determined in plasma SCUBE1 levels of the rats exposed to torsion. In addition, there was no statistically significant difference between TT group plasma SCUBE1 levels and those of the control group. Türedi et al. (11) reported a significant correlation between TT SCUBE1 levels and histopathological scores. In our study, however, no significant correlation was observed between TT SCUBE1 levels and histopathological scores. In contrast to Türedi et al.'s (11) study, which reported that measurement of plasma SCUBE1 levels could be of diagnostic, therapeutic, or prognostic values in TT, we concluded that these are of no diagnostic value.

Complement 3a and complement 5a, chemotactic factors that appear in the ischemic area in TT, cause neutrophils to migrate to the region (10). Prochemerin is converted into chemerin with cathepsin G and neutrophil elastase released from activated neutrophil granules. Chemerin performs a chemotactic function for cells producing antibodies in inflammation or tissue injury. CMKLR1 stimulates chemotaxis of expressing dendritic cells macrophages and enables these cells to be directed to the area of inflammation (7, 9). Goralski et al. (18) reported that chemerin and CMKLR1 expression in epididymal white adipose tissue was twice as high compared to stromal vascular fraction.

Kadoglou et al. (19) reported an in increase in chemerin levels in a study of patients with acute myocardial infarction (AMI). Ji et al. (20) reported that plasma chemerin levels increased in patients with ACS, with the exception of stable angina pectoris. In a clinical study, Zhao et al. (21) reported an increase in plasma chemerin levels with AIS and carotid artery atherosclerosis. Chemerin levels in atherosclerosis increased in correlation with plaque instability and were higher in AIS. Zhao et al. (21) examined serum chemerin levels in patients with AIS and carotid artery atherosclerosis and investigated whether chemerin elevation might be a possible risk factor for these diseases. In the same clinical study, chemerin levels increased in correlation with plaque instability in carotid artery atherosclerosis and were higher in AIS. The authors concluded that chemerin levels might play an indicative role in monitoring the development of atherosclerosis and cerebral infarction.

In our study, chemerin levels decreased as the duration of torsion ischemia increased. We attributed this to the development of torsion ischemia not being vascular plaque--dependent. In an experimental study of intestinal ischemia-reperfusion injury induced in mice by blocking the mesenteric artery, Zhu et al. (22) reported a significant increase in plasma chemerin levels after 60-min reperfusion following 60-min ischemia. A statistically significant change was determined in chemerin levels in rats subjected to torsion in our study. This was statistically significant between the 2-h (group II) and 4-h (group III) TT groups. However, no statistically significant difference was determined between the plasma chemerin levels of torsion groups and those of the control group. At histopathological scoring, there was a statistically significant difference between the TT group grades. However, there was no significant difference between group I and II TT grades. Also, there was no significant correlation determined between TT plasma chemerin levels and histopathological scores. The reason for the absence of a statistically significant difference with the control group, although chemerin levels decreased, is that vascular coagulation did not occur during the TT process. Our study did not investigate chemerin levels after 4 h following torsion ischemia. We therefore think that wider studies are now needed in human patients.

### Study limitations

Prepubertal rats were used in this study, as TT is more commonly seen in very young males. Hematological status in prepubertal rats may differ in various ways compared to adult rats and in humans. At the same time, the experimental model may not exactly mimic typical cases of TT seen in clinical practice. We measured chemerin and SCUBE1 levels by exposing rats to experimental torsion for 30 min and 2 and 4 h. Plasma levels of these markers were not measured in the long-term after torsion ischemia. While reperfusion injury following detorsion is known to be as significant a factor as ischemia in patients with TT, detorsion was not applied in this experimental model.

## Conclusion

We observed no statistically significant differences when plasma SCUBE1 and chemerin levels of rats subjected to TT were compared with a control group in this study.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Istanbul University Animal Experiments Local Ethical Committee (No. 2015/67).

**Peer-review:** Externally peer-reviewed.

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

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# Diagnostic Value of Cyclophilin A in Acute Ischemic Stroke

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## Abstract

**Aim:** The early diagnosis and treatment of patients presenting to the emergency department symptoms of stroke can significantly reduce mortality and morbidity rates associated with it. This study aimed to investigate the diagnostic value of serum yclophilin A levels in our study group who presented to the emergency department with symptoms of acute ischemic stroke.

**Materials and Methods:** In total, 114 patients diagnosed with acute ischemic stroke between October 2013 and October 2014 and a control group of 66 healthy volunteers were included. Cyclophilin A levels in the patient and control groups were compared.

**Results:** The median cyclophilin A levels in the patient and control groups measured at the time of presentation were 13.47 (11.97–17.92) ng/mL and 11.54 (8.48–16.22) ng/mL, respectively. These levels were significantly higher in the patient group than in the control group ($p<0.05$).

**Conclusion:** Plasma cyclophilin A levels were significantly higher in the patient group than in the control group.

**Keywords:** Acute ischemic stroke, cyclophilin A, emergency department

## Introduction

The most important cause of ischemic stroke is atherothrombotic events. Atherosclerosis is a systemic disease of medium- and large-diameter elastic and muscular arteries and can lead to ischemia and infarction in the brain, heart, and extremities. Systemic inflammation has been shown to be involved in every stage of the development of atherosclerosis (1, 2). Hypoxia and, therefore, oxidative stress increase in patients with acute ischemic stroke. Cyclophilin A is a protein exhibiting peptidyl–prolyl cis–trans isomerase activity because of which it assists in protein folding (3). Cyclophilin A, which is an intracellular protein, is released from smooth muscle cells and macrophages in response increased oxidative stress. It exhibits pro-inflammatory effects on endothelial cells and plays an important role in the pathogenesis of inflammatory diseases (4). Cyclophilin A is regarded as a biomarker whose levels rise in platelet activation during acute thrombotic complications. The current study aimed to determine cyclophilin A levels in patients presenting to the emergency department and with the diagnosis of acute ischemic stroke and to investigate this parameter in terms of its diagnostic value in acute ischemic stroke.

## Materials and methods

### Study design and settings

This research was planned as a multicenter, prospective, time-limited study. Following local ethical committee approval, 114 patients presenting to a tertiary university education and research hospital with symptoms of stroke and diagnosed with acute ischemic stroke following brain diffusion magnetic resonance imaging over a

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12-month period were included. Sixty-six healthy volunteers with similar demographic characteristics to patients in the patient group were enrolled in the control group. Patients aged 18 years or over, with a confirmed diagnosis of acute ischemic stroke in the emergency department, and who provided consent were enrolled. Patients with acute coronary syndrome, hemorrhagic stroke, liver failure, acute kidney failure, sepsis, acute pulmonary edema, acute peripheral artery disease, pulmonary thromboembolism, acute mesenteric ischemia, cardiopulmonary arrest, or multi-trauma were excluded.

**Blood sample measurement of cyclophilin A levels**

In total, 5 mL of blood was placed into vacuum separator tubes without an anticoagulant. After being stored at room temperature for approximately 30 min, the samples were centrifuged at 3000 rpm for 10 min. Separated serum samples were then placed into 1.5 mL Eppendorf tubes and kept at −80°C until measurement. Cyclophilin A levels were calculated using a commercial CUSABIO (catalog no: CSB-E09920h) enzyme-linked immunosorbent assay (ELISA) kit in line with the manufacturer's instructions. Levels are expressed as ng/mL.

**Statistical analysis**

Statistical analysis was performed using Statistical Package for Social Sciences 13.0 for windows v.13.0 (SPSS Inc.; Chicago, IL, USA). Non-parametric variables were calculated as median (interquartile range). Parametric variables were calculated as mean and standard deviation. Non-parametric tests were used to analyze data. The Mann–Whitney U test was used to compare the median values in the groups. Correlations between variables were evaluated using Spearman correlation analysis. Receiver operating characteristic (ROC) curves were used to assess the sensitivity and specificity of serum cyclophilin A levels. P values of <0.05 were considered to be statistically significant.

## Results

The demographic and biochemical characteristics of the patient and control groups are shown in Table 1. The median cyclophilin A levels in the patient group measured at the time of presentation to the emergency department were 13.47 (11.97–17.92) ng/mL; the median levels were 11.54 (8.48–16.22) ng/mL in the control group ($p<0.05$). The median levels in the ischemic stroke and control groups are shown in Figure 1. Spearman correlation analysis performed to examine the relationship between age and cyclophilin A levels revealed no significant correlation between the patient group and the control group ($p>0.05$). In ROC analysis that was performed to investigate the diagnostic value of cyclophilin A in patients with acute ischemic stroke, the area under the curve was determined to be 0.630 (95% confidence interval, 0.579–0.720) (Figure 2). When the level of cyclophilin A at 12.2 ng/mL, the sensitivity was calculated 55% and specificity was calculated 70%. while diagnosing for acute ischemic stroke.

**Table 1.** Demographic and biochemical features of the study population

| | Stroke | Control | p |
|---|---|---|---|
| Age, years | 68.2±15.3 | 61.7±9.7 | 0.001 |
| Gender, female (%) | 51.8 | 42.4 | 0.23 |
| Cyclophilin A (ng/mL)* | 13.47 (11.97–17.92) | 11.54 (8.48–16.22) | 0.004 |
| *Values are reported as median (25%–75%) | | | |

## Discussion

This study showed that plasma cyclophilin A levels increase in the event of ischemic stroke. Recent studies have shown changes in the levels of cyclophilin A in coronary artery disease and aortic aneurysm (5-7). Some studies have shown that cyclophilin A levels increase during oxidative stress and inflammation (8-10). Studies on the subject refer to the interaction between endothelial cells in the arterial wall and vascular smooth muscle cells playing an important role in ensuring vascular integrity. Reactive oxygen species (ROS) have been reported to be released from vascular smooth muscle cells

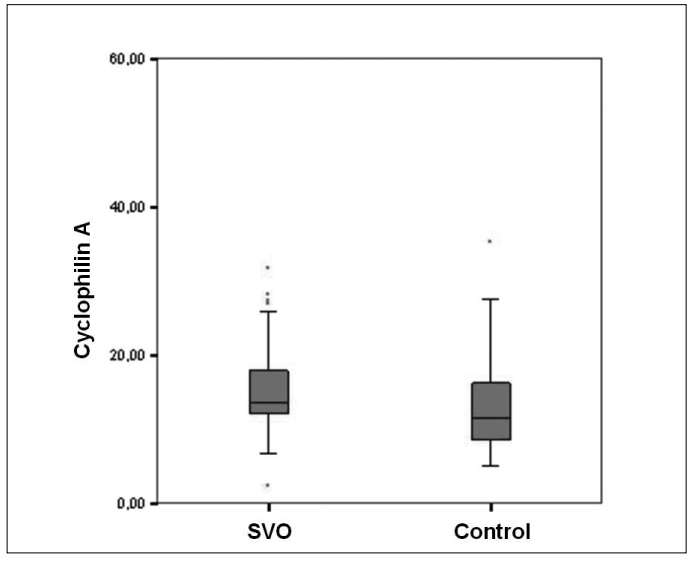


**Figure 1.** Median levels in the ischemic stroke and control groups shown in a box plot

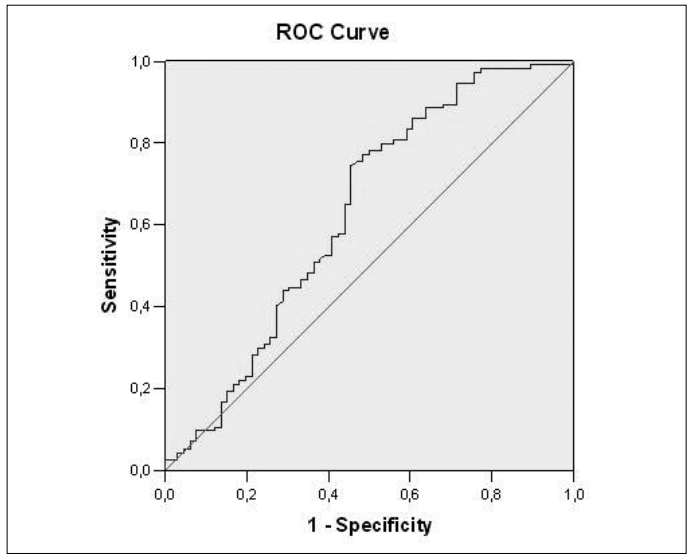


**Figure 2.** Receiver operating characteristic curve analyses of the diagnostic value of plasma cyclophilin A in ischemic stroke

under oxidative stress (11, 12). ROS induce the release of cyclophilin A from endothelial cells (10, 11). Cyclophilin A induces the formation of adhesion molecules from endothelial cells and causes övascular smooth muscle cells to multiply and migrate (4). Cyclophilin A is also involved in the activation of matrix metalloproteins, which are chemoattractants for inflammatory cells (13, 14). Cyclophilin A therefore plays a key mediator role in affecting endothelial cell, vascular smooth muscle cell, and inflammatory cell functions in oxidative stress. In a study on patients with diabetes mellitus (DM), Ramachandran et al. (15) determined higher cyclophilin A levels in patients with DM than in controls. In their immunohistochemical investigation of synovial fluid from patients with rheumatoid arthritis, Ho Kim et al. detected cyclophilin A in endothelial cells, particularly macrophages, lymphocytes, and smooth muscle cells. (14). A study by Satoh et al. (16), support the idea that cyclophilin A levels increases during inflammatory processes. One study involving patients with coronary artery disease had significantly higher cyclophilin A levels in patients with stenosis than in those without (16). Yan et al. (17) investigated the prognostic value of cyclophilin A in patients with coronary syndrome and reported significantly higher levels of cyclophilin A in patients with acute myocardial infarction and unstable angina pectoris than in patients with stable angina pectoris and healthy subjects. The same study also identified a powerful correlation between cyclophilin A levels and complex coronary stenosis (17). In their histopathological examination of patients with inflammatory or non-inflammatory cardiomyopathy, Seizer et al. (18) did not detect cyclophilin A in patients with non-inflammatory cardiomyopathy but detected it in patients with inflammatory cardiomyopathy. In our study, we attributed the significantly higher cyclophilin A levels in the patient group than in the control group to occlusion occurring due to inflammation against an atherosclerotic background.

### Study limitations

One of the limitations of this study is the small number of patients. Patients were also differentiated in terms of etiology. As not all ischemic strokes occur against an atherosclerotic and inflammatory background, cyclophilin A levels may be normal in patients with cardioembolic stroke in particular. Further studies examining cyclophilin A levels in ischemic stroke subgroups may therefore be needed.

## Conclusion

Evaluation of the studies in the literature and our research reveals a significant increase in plasma cyclophilin A levels due to atherosclerosis and inflammation. Our study may be considered a pioneering work in the field of acute stroke management and can serve as a basis for further comprehensive studies. Cyclophilin A levels can assist in the diagnosis of patients presenting to the emergency department with ischemic stroke.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Karadeniz Technical University (The approval no was 2013-92).

**Informed Consent:** Written informed consent was obtained from the patients and patients' parents who participated in this study.

**Peer-review:** Externally peer-reviewed.

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

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# Are There any Predictive Values of Mean Platelet Volume (MPV) and MPV/Platelet Count Ratio in Patients with Spontaneous Abortion?

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## Abstract

**Aim:** The objective of this study was to evaluate the predictive value of mean platelet volume (MPV) and MPV/platelet count ratio and to determine whether they are based on hemoconcentration in patients with spontaneous abortions.

**Materials and Methods:** A total of 271 women with singleton pregnancies between January 1, 2012, and June 30, 2012, were included (171 healthy pregnant, 200 spontaneous abortion). Study data were obtained from hospital data processing system, emergency department charts, and consultation records. Mann-Whitney U, Kruskal-Wallis H (post-hoc Bonferroni-corrected Mann-Whitney U), and logistic regression (LR forward method) analyses were used as appropriate.

**Results:** Among the patients with MPV>9.1 fl, it was observed that they had a greater rate of spontaneous abortions with vaginal bleeding. The levels of hemoglobin, hematocrit, urea, and creatinine as well as platelets count were significantly higher in women with a spontaneous abortion ($p<0.05$). There were no significant differences between abortion subgroups with bleeding and non-bleeding symptoms ($p>0.05$).

**Conclusion:** These results suggest that minimal changes in both MPV and MPV/platelet count ratio can aid the clinician during routine pregnancy visits or in the emergency department by serving as indicators of an increased risk of abortion, but more importantly the elevated hemoglobin despite bleeding strongly suggests hemoconcentration possibility.

**Keywords:** Emergency, pregnancy, routine laboratory, spontaneous abortion

## Introduction

Pregnancy is a normal physiological phenomenon with many biochemical changes. Nevertheless, early pregnancy loss is a common complication of pregnancy, with an incidence of 50%–70% (1-3). The World Health Organization (WHO) has defined spontaneous abortion as the loss of a fetus before 20 weeks or that is weighing less than 500 grams (4). More than 60% of spontaneous abortions are due to maternal or paternal chromosomal abnormalities and 15% are due to maternal trauma, infections, dietary deficiencies, diabetes mellitus, hypothyroidism, lupus anticoagulant-anticardiolipin-antiphospholipid antibody syndrome, advanced maternal age, toxic effects, or anatomic disorders. Nevertheless, one quarter of cases have no clear cause (4). Blood tests are routinely used to identify metabolic abnormalities that reflect conditions harmful to the mother or fetus, but routine laboratory reference values may not reflect natural alterations of pregnancy. There are few reports of first and second trimester normal reference intervals for pregnant women (2, 5, 6). Indeed, biochemical changes associated with pregnancy that assist the development and survival of the fetus can alter laboratory values so they fall outside the normal, non-pregnant range and are thus misinterpreted as abnormal (1). It is critical to characterize the normal and abnormal changes of pregnancy, as laboratory results are often used to influence management of both the mother and the child (1). Without appropriate reference ranges, there is both an increased risk of missing important changes due to pathological conditions and a risk of erroneously interpreting normal changes as pathological events (5).

Many previous studies have identified normal pregnancy laboratory reference values, determined pregnancy-related changes in organ function, and studied special biomarkers, but no studies have heretofore compared laboratory values in women with spontaneous

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abortion to values in healthy pregnant women (2, 6). Comparing laboratory results of women with a spontaneous abortion to results of normal pregnant women at the same gestational age may more clearly identify laboratory risk factors for abortion than comparing them to the normal reference values of non-pregnant women. However, there is no predictive factor to estimate spontaneous abortions yet.

The objective of this study was to evaluate the predictive value of mean platelet volume (MPV) and MPV/platelet count ratio and to determine whether they are based on hemoconcentration in patients with spontaneous abortions.

## Materials and Methods

This study was approved by our Local Research Ethics Committee (No. 9). Of the 2738 women examined in the Ataturk Research and Training Hospital Emergency Department of Katip Celebi University (Izmir, Turkey) between January 01, 2012, and June 30, 2012, data were retrospectively collected from 171 normal, healthy pregnant women in the first 20 weeks of gestation and 200 women with spontaneous abortion. Only women with singleton pregnancies were included.

Normal pregnancy was defined as a pregnancy with no evidence of maternal or fetal disease, in which the mother did not take medications or exhibit abnormal vaginal bleeding or other pregnancy-related complications throughout the pregnancy. Additional inclusion criteria for the healthy pregnancy group were a normal outcome of the pregnancy and all follow-up conducted at our hospital. Only women with totally uncomplicated pregnancies were included in this group to ensure that the results were not influenced by any pathological condition. The abortion group included women in whom a gynecologist/obstetrician diagnosed imminent abortion, abortion incipience, incomplete abortion, complete abortion, missed abortion, or septic abortion. Gestational age was estimated by the crown--rump length, as determined by an ultrasound scan performed by the attending obstetrician (Sonoace X8, Medison Inc., Seoul, Korea). In cases with no signs of conception, the gestational age was determined according to the date of the last menstrual period.

Obstetrical history, physical examination, and other clinical data were obtained from the emergency department charts and obstetrics consultation records.

Laboratory variables used were: levels of hemoglobin (Hb, g/fL), hematocrit (Hct, %), urea (mg/dL), and creatinine (mg/dL) as well as counts of white blood cells (WBC, K/mL**)** and platelets (Plt, K/mL) in addition to MPV (fl) and MPV/platelet counts ratio.

All blood laboratory samples were analysed for complete blood count, routine biochemistry, and basic coagulation tests in the same laboratory. Levels of Hb and Hct and counts of WBC and Plt as well as MPV testing were performed using the Automated Hematology Analyser (Cell-Dyn 3700 Abbott, Abbott Park, IL). Biochemical tests including urea and creatinine levels were conducted with an autoanalyzer (C16000; Abbott).

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) version 15.0for Windows program, with 95% confidence intervals. The distribution of the data was tested by applying the Kolmogorov-Smirnov and Shapiro-Wilk tests of normality. The variables failed to show a normal distribution ($p<0.05$); therefore, non-parametric tests were used. The Mann-Whitney U test was used for the comparison of two groups of continuous data. The Kruskal-Wallis H (post-hoc Bonferroni-corrected Mann-Whitney U) test was used to compare more than two groups, the results of one-way analysis of variance comparing all laboratory blood test parameters between abortion subgroups are shown. Otherwise the cut-off value of the MPV was calculated with receiver operator characteristics (ROC) curve analyses. The standard deviation and 95% confidence intervals for the mean were determined for all laboratory parameters. Logistic regression (LR forward method) analyses were performed to determine the effect of variables on the occurrence of a spontaneous abortion. Statistical significance was defined as $p<0.05$.

## Results

This study included 371 women: 200 in the abortion group and 171 in the healthy pregnancy group. The diagnoses for the abortion cases were distributed as follows: abortion imminence, 36% (n=72); missed abortion, 23.5% (n=47); incomplete abortion, 27.5% (n=55); complete abortion, 7.5% (n=15); and abortion incipience, 5.5% (n=11). The abortion group was also divided into bleeding (n=179, 89.5%) and non-bleeding (n=21, 10.5%) subgroups, based on their symptoms upon arrival in the emergency room.

The patients' baseline characteristics are listed in Table 1. Mean age, number of pregnancies, number of births, and number of previous abortions were significantly higher in the abortion group than in the healthy pregnancy group ($p<0.05$), and the gestational age of the abortion group was significantly lower than the healthy pregnancy group ($p<0.001$). Post-hoc Bonferroni-corrected Mann-Whitney U

**Table 1.** Patient characteristics: age, number of pregnancies, number of births, and number of previous abortions

| | Abortion group | | | Healthy pregnancy group | | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean±SD | Min | Max | Mean±SD | Min | Max | Mean±SD | Min | Max | p* |
| Age (y) | 28.76±6.52 | 17 | 46 | 25.5±5.5 | 16 | 42 | 27.25±6.28 | 16 | 46 | <0.001 |
| Gestational age (days) | 66.59±25.89 | 20 | 147 | 81.21±33.35 | 14 | 144 | 73.27±30.38 | 14 | 147 | <0.001 |
| Number of pregnancies | 2.48±1.6 | 1 | 9 | 2.01±1.3 | 1 | 7 | 2.26±1.48 | 1 | 9 | 0.002 |
| Number of births | 1.05±1.25 | 0 | 8 | 0.78±1.03 | 0 | 4 | 0.93±1.16 | 0 | 8 | 0.031 |
| Number of prior abortions | 0.46±0.96 | 0 | 8 | 0.22±0.53 | 0 | 3 | 0.35±0.8 | 0 | 8 | 0.003 |

*Mann-Whitney U test. Max: maximum; Min: minimum; SD: standard deviation

**Table 2.** Distribution of blood laboratory values of the abortion and healthy pregnancy groups

| | Abortion group | | Healthy pregnancy group | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p* |
| WBC (K/µL) | 10.06 | 3.17 | 9.35 | 1.71 | 0.282 |
| Hb (g/dL) | 12.39 | 1.24 | 11.94 | 1.01 | <0.001 |
| Hct (%) | 35.85 | 3.19 | 35.31 | 12.03 | <0.001 |
| Plt (K/µL) | 271.44 | 64.27 | 247.72 | 55.41 | <0.001 |
| MPV (fL) | 8.60 | 1.43 | 8.39 | 1.36 | 0.433 |
| MPV/platelets count ratio | 0.03 | 0.00011 | 0.04 | 0.00101 | <0.001 |
| Urea (mg/dL) | 8.98 | 2.85 | 8.36 | 2.44 | 0.039 |
| Creatinine (mg/dL) | 0.59 | 0.07 | 0.56 | 0.07 | <0.001 |

*Mann-Whitney U test. SD: standard deviation; WBC: white blood cell; Hb: hemoglobin; Hct: hematocrit; Plt: platelet; MPV: mean platelet volume

**Table 3.** Distribution of blood laboratory values of abortion cases based on their bleeding status at emergency room arrival

| | Bleeding (n=179) | Non-bleeding (n=21) | |
|---|---|---|---|
| | Mean±SD | Mean±SD | p* |
| WBC (K/L) | 10.12±3.23 | 9.41±2.65 | 0.480 |
| Hb (g/dL) | 12.34±1.28 | 12.89±0.75 | 0.093 |
| Hct (%) | 35.73±3.28 | 37.02±1.92 | 0.096 |
| Plt (K/L) | 269.56±64.32 | 287.75±64.71 | 0.193 |
| MPV (fL) | 8.63±1.47 | 8.33±1.03 | 0.451 |
| MPV/platelets count ratio | 0.03±0.00024 | 0.03±0.00018 | <0.001 |
| Urea (mg/dL) | 9.13±2.91 | 7.50±1.64 | 0.007 |
| Creatinine (mg/dL) | 0.59±0.07 | 0.56±0.06 | 0.133 |

*Mann-Whitney U test. SD: standard deviation; WBC: white blood cell; Hb: hemoglobin; Hct: hematocrit; Plt: platelet; MPV: mean platelet volume

tests of baseline characteristics for the abortion subgroups revealed no significant differences between subgroups for mean age, gestational age, number of pregnancies, and number of previous abortions (p>0.05), although the number of births was significantly higher in the incomplete abortion group than in the complete abortion group (p<0.05).

As noted in Table 2, Hb, Hct, Plt, urea, and creatinine values were significantly higher in the abortion group than in the healthy pregnancy group (p<0.05). However, the MPV values were not significantly different between the two groups (p>0.05). Otherwise, the MPV/platelet count ratio levels were significantly lower in the abortion group than in control group (p<0.05).

The laboratory results of the bleeding and non-bleeding groups were compared with the Mann-Whitney U test to help understand the association between bleeding and the abortion process (Table 3). Urea levels were significantly higher in the bleeding group but MPV/platelet count ratio was significantly lower in this group (p<0.05 and p<0.05, respectively).

Cut-off value for MPV was taken as 9.1 fL, and the patients were divided in two groups. According to this classification, patients with MPV value higher than 9.1 fL have suffered from spontaneous abortion with bleeding (p>0.05). Moreover, it was defined a positive and significant correlation between higher levels than 9.1 fL of the MPV and increased urea (r=0.621, p=0.031), creatinine (r=0.539, p=0.037), Hb (r=0.648, p=0.018), Hct (r=0.496, p=0.042) levels, decreased MPV/platelets count ratio (r=0.598, p=0.029), and spontaneous abortions with bleeding (r=0.618, p=0.024).

According to the cut-off level of MPV, we found that MPV levels higher than 9.1 fL had been seen a 85% specificity, 91% sensitivity, 94% accuracy, 61% negative likelihood value, and 74% positive likelihood value to predict to patients who had spontaneous abortion with bleeding.

The results of one-way analysis of variance comparing all laboratory blood test parameters between abortion subgroups are shown in Table 4.

LR analysis with a forward LR method identified parameters that affected the occurrence of abortion (Table 5).

**Table 4.** Distribution of blood laboratory values of the abortion subgroups

| | Diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | Abortion imminence | Missed abortion | Incomplete abortion | Complete abortion | Abortion incipience | |
| | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | p* |
| WBC (K/L) | 9.8±3.44 | 10.31±3.07 | 10.24±3.31 | 9.8±2.39 | 10.11±2.10 | 0.462 |
| Hb (g/dL) | 12.27±1.35 | 12.48±1.29 | 12.41±1.19 | 12.42±0.94 | 12.58±1.05 | 0.824 |
| Hct (%) | 35.67±3.35 | 36.05±3.61 | 35.93±2.84 | 35.91±2.77 | 35.71±2.86 | 0.927 |
| Plt (K/L) | 261.98±65.67 | 282.34±65.26 | 276.38±63.64 | 270.47±62.79 | 263.36±56.46 | 0.493 |
| MPV (fL) | 8.59±1.69 | 8.62±1.36 | 8.38±1.13 | 8.54±1.11 | 9.7±1.34 | 0.071 |
| MPV/platelets count ratio | 0.03±0.00012 | 0.03±0.00023 | 0.03±0.00019 | 0.03±0.00016 | 0.03±0.00019 | 0.068 |
| Urea (mg/dL) | 9.06±3.34 | 9.33±2.49 | 8.80±2.82 | 9.27±1.83 | 7.64±1.69 | 0.266 |
| Creatinine (mg/dL) | 0.59±0.07 | 0.59±0.07 | 0.59±0.08 | 0.62±0.08 | 0.59±0.07 | 0.744 |

*Kruskal–Wallis H test. SD: standard deviation; WBC: white blood cell; Hb: hemoglobin; Hct: hematocrit; Plt: platelet; MPV: mean platelet volume

**Table 5.** LR analysis (forward LR) of variables associated with the risk of an abortion

| Variable | B | Standard error | Wald | df | Significance | Exp(B) * | 95% C.I. for Exp(B) | |
|---|---|---|---|---|---|---|---|---|
| Maternal age | 0.103 | 0.024 | 18.813 | 1 | <0.001 | 1.108 | 1.058 | 1.161 |
| Gestational age | -0.014 | 0.005 | 7.318 | 1 | 0.007 | 0.986 | 0.977 | 0.996 |
| WBC | 0.157 | 0.061 | 6.681 | 1 | 0.010 | 1.170 | 1.039 | 1.318 |
| Hb | 0.316 | 0.134 | 5.523 | 1 | 0.019 | 1.372 | 1.054 | 1.785 |
| Plt | 0.006 | 0.002 | 6.641 | 1 | 0.010 | 1.006 | 1.002 | 1.011 |
| MPV/platelets count ratio | 0.008 | 0.002 | 6.514 | 1 | 0.000 | 1.011 | 1.004 | 1.018 |
| Constant | -39.927 | 7.913 | 25.459 | 1 | 0.000 | 0.000 | | |

*Exp(B) represents the odds ratio. CI: confidence interval; df: degree of freedom; SD: standard deviation; WBC: white blood cell; Hb: hemoglobin; Plt: platelet; MPV: mean platelet volume

## Discussion

Blood tests were often recommended during pregnancy. The laboratory reference intervals were usually based on the results of tests obtained in healthy or non-pregnant women. This is not optimal, as many biological markers change during pregnancy, and using the most appropriate reference values is necessary to make correct clinical decisions (5-8).

During normal pregnancy, an increased cardiac output was found to improve renal perfusion, which led to an increased glomerular filtration rate (GFR), compared to pre-pregnancy values. The increase in GFR was observable within 1 month of conception, peaked at approximately 40%–50% above baseline by the early second trimester, and then declined slightly near the end of pregnancy (9). Increased GFR led to lower serum creatinine and urea levels in pregnant women (5, 10, 11). Indeed, even in the presence of severe proteinuria, serum urea, and creatinine usually remained within the normal range during pregnancy (12, 13). Our findings that the urea and creatinine levels were statistically higher in the abortion group than in the healthy pregnancy group suggest that renal adaptation is less pronounced in women undergoing spontaneous abortion than in healthy pregnant women.

The WHO defines anemia in pregnant women as an Hb<110 g/L or a Hct<6.83 mmol/L or <33% (9). Neither of the study groups was anemic according to this definition, but significantly higher Hb, Hct, and Plt values were found in the abortion group. These findings were noted, despite the observation that almost 90% of the abortion group presented with bleeding symptoms. This suggests that hemoconcentration may have been present in the abortion group. Maternal hemoconcentration and high viscosity have been previously reported during severe pre-eclampsia; they may further impede the uteroplacental blood flow that is already compromised by pre-eclampsia, thereby contributing to placental infarction and growth retardation or fetal death (14, 15). Blood viscosity reaches a level that impairs microcirculation, and an inadequate amount of oxygen is transported to tissues, similar to the situation with severe anemia (16). Contracted plasma volume resulted in an appearance of greater red cell volume. The principal mechanism for perinatal morbidity and mortality due to pre-eclampsia-such as pregnancy-induced hypertension-is poor placental and fetal perfusion (16).

In normal pregnancy, Plt counts are similar to or slightly lower than those observed in healthy subjects (17). The Plt and Pct levels were higher in our abortion group, but the MPV values were not statistically different between the abortion and healthy pregnancy groups, and there were no statistically significant differences between the abortion subgroups. In contrast, Kosus et al. (2) reported higher MPV values in patients with a missed abortion than in those with a healthy pregnancy. Larger platelets, reflecting higher MPV values, are hemostatically more reactive than smaller platelets and thus have a greater propensity to form thromboses (18). These modifications of the coagulation system result from hormonal changes and are part of a complex physiological adaptation of the organism to pregnancy (19). However, the constant MPV, reflecting the presence of less active platelets, may represent a pre-disseminated intravascular coagulation state or activation of the fibrinolytic system as part of the spontaneous abortion process (20).

Strengths of this study include its blinded collection and interpretation of the data, as well as its large sample size, which give our results narrow confidence intervals. Furthermore, we compared the abortion group with a healthy pregnancy group, whose similar physiological baseline provided a more appropriate comparison than a non-pregnant population. Although there were statistically significant differences in gestational age between patients in the abortion and healthy pregnancy groups, this was likely of no clinical relevance, as the difference between groups was only a few days, and patients in both groups were in the same trimester.

### Study limitations

A limitation of the study became evident when we noted that the Hb and Hct levels were elevated in the abortion group despite the presence of vaginal bleeding. Although these elevations suggest the presence of hemoconcentration in the abortion group, it is not possible to determine whether hemoconcentration was the result or cause of the abortion because we were unable to compare the abortion group laboratory values to those obtained from the same patients prior to their abortion. Further studies would be required to more fully address this issue.

## Conclusion

Laboratory parameters of healthy pregnant women should reflect the physiological changes during pregnancy. Our results demonstrate small, although significant, differences in MPV level and MPV/platelet ratio as well as some variables probably related with hemoconcentration such as Hb, Hct, urea, creatinine levels, and Plt count between the abortion and healthy pregnancy groups. These results may assist clini-

cians, as the observed changes in routine parameters during routine pregnancy visits may identify risk factors for abortion. Although there are various statistical differences in the results of our study, they are so small and within the error range of the laboratory measurements. They probably have no practical significance, but the most important point in these results has been indicated that there is a marked finding about hemoconcentration according these results. Moreover, this situation can be associated with poor fetal outcome, and it can be an avoidable subject especially for imminent abortion. Although statistically significant differences were noted, further studies are required to identify clinically useful cutoffs for these parameters.

**Ethics Committee Approval:** This study was approved by the Katip Celebi University Ataturk Research and Training Hospital Research Ethics Committee (date of approval: 04.01.2013, No. 9).

**Informed Consent:** There is no need for informed consent because it is a retrospective data study.

**Peer-review:** Externally peer-reviewed.

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

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

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# Role of CA125 in the Diagnosis of Acute Appendicitis

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## Abstract

**Aim:** Acute appendicitis (AA) is the most common surgical emergency in the world, and its diagnosis is mainly dependent on clinical findings. Recently, secretion of CA125 from peritoneal cells due to inflammatory stimulus has been shown. The aim of this study was to evaluate the relation between CA25 levels and AA.

**Materials and Methods:** In this prospective trial, CA125 levels were measured. Group 1 consisted histopathologically approved AA cases. Group 2 consisted healthy individuals.

**Results:** Seventy-four cases (37 AA and 37 healthy individuals) were included in the study. In the AA group, the mean CA125 level was 9.8±9.3 U/mL, and in the control group, it was 4.6±1.5 U/mL. In Pearson correlation analysis, the CA125 level had a positive correlation with AA (r=0.371, p=0.001).

**Conclusion:** Recent studies demonstrate that CA125 can help distinguish patients with or without AA. CA125 levels can be used as a marker of AA in cases with clinical doubt.

**Keywords:** Acute appendicitis, diagnosis, CA-125

## Introduction

Acute appendicitis (AA) is the most common surgical emergency in the world (1). Diagnosis of AA mainly depends on clinical findings. Laboratory markers and radiological studies play only a supportive role. Although developments in clinical, laboratory, and radiologic tools, negative appendectomy rate is still 15% (2). There are several markers are still being researched for correlation of definitive diagnosis of AA. Mainly leukocyte number and C-reactive protein are used for laboratory markers. However, they only show inflammation and are not specific to AA (3, 4). There is still no specific laboratory or clinical marker of AA.

Recently, a number researches are made for improving the medical treatment of AA (5-8). In such an era of medical treatment, definitive diagnosis plays a very important role. Recent data support evidence of successful medical treatment of uncomplicated AA cases. However, the main problem in these reports is that the exact number of negative appendicitis cases in medical treatment arm is not known.

CA125 is a glycoprotein secreted from mesothelial cells. It is mainly used in the diagnosis and post-op follow-up of gynecological tumors. In males, the main source of CA125 is liver cirrhosis (9). Recently, secretion of CA125 from peritoneal cells due to inflammatory stimulus has been shown. Although there are a few of studies showing the relation between CA125 and AA, the evidence is not strong enough for the routine use of CA125 in cases suspected of AA.

The aim of this study was to evaluate the relation between CA125 levels and histopathologically approved AA.

## Materials and Methods

For this prospective controlled study, ethical approval was obtained from ethics committee of the Selçuk University Medical School (Date: December 24, 2013; number: 2013/378). The study was conducted at a tertiary training and research hospital between February 2014 and February 2015.

For the power analysis, the CA125 levels reported by Berger et al. (10) were considered. According to Berger et al. (10), the mean CA125 levels of patients with and without AA were 9.9±4.7 and 7.8±3.2 U/mL, respectively. In the power analysis, we used those levels. With a power of 80% and a beta error of 0.05, we had to include 37 cases in each group.

To exclude the effect of ovarian disorders and fluctuations during menstrual cycles on CA125 levels, only male cases were included in this study.

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Male patients admitted to the surgery department with diagnosis of AA were considered for the study. After informed consent, serum samples from all the cases with clinical diagnoses of AA were obtained and stored. Only the cases with histopathologically approved AA were included in the study. Cases operated for clinical diagnosis of AA, but not histopathologically proven AA were not included in the study. CA125 levels in cases with definitive diagnosis of AA were measured.

For the control group, serum samples from healthy volunteers were obtained, and CA125 levels were measured.

**Statistical analysis**

For statistical analysis, IBM Statistical Package for the Social Sciences (IBM SPSS Statistics; Armonk, NY, USA) 20 package software was used. Data was presented as mean ± standard deviation (SD). In comparison of the groups, the Student t-test was used. For determination of correlation, Pearson correlation analysis was used and correlation coefficients are presented. CA125 values in predicting AA were analyzed using receiver operating characteristics (ROC) curve analysis. When a significant cutoff value was observed, the sensitivity and specificity were presented. Statistical significance level (p-value) was accepted as 0.05.

## Results

Seventy-four male subjects were included in the study. There were 37 AA cases in the study group and 37 healthy volunteers in the control group. The mean age of the patients was 27.7±8.4 years. The groups were similar in terms of mean age [29.6±11.03 and 25.9±4 years, respectively (p=0.61)]. Demographic data, mean hemoglobin and leukocyte counts, and CA125 levels are presented in Table 1. The distribution of the pathological diagnosis of the operated cases are presented in Table 2.

The mean CA125 level was 9.8±9.3 U/mL in the AA group and 4.6±1.5 U/mL in the control group (Figure 1). The difference between the groups was statistically significant (p=0.001). In Pearson correlation analysis, the CA125 level had a positive correlation with AA (r=0.371, p=0.001).

According to the ROC curve, the optimal CA125 value for AA was found to be 5.22 U/mL with a sensitivity of 81% and specificity of 65% (AUC=0.795, p<0.001) (Figure 2).

## Discussion

The present study evaluated the relation between CA125 levels and AA. The results demonstrate a significant increase in CA125 levels in cases with AA and a significant decrease in CA125 levels after appendectomy.

Acute appendicitis is the most common surgical emergency. If untreated, it may cause complications and mortality. Complicated AA comprises 18–34% of cases (11, 12). Main complications are perforation and abscess formation. A delay in diagnosis can result in perforation rates as high as 80% (13, 14). Perforation may lead to peritonitis and even sepsis and death. Diagnosis of AA mainly depends on clinical findings. Laboratory and imaging studies can be used as accessory modalities. Ultrasonography and computed tomography are commonly used imaging studies. The sensitivity and specificity of ultrasonography are 99.1% and 91.7%, respectively. For computed tomography, sensitivity is reported as 96.4% and specificity is reported as 95.4% (15). There are several laboratory markers evaluated for the diagnosis of AA. C-reactive protein and leukocyte counts are

**Table 1.** Demographic data, mean hemoglobin, leukocyte count, and CA125 levels of the cases and controls

| | Case | Control | p* |
|---|---|---|---|
| Age (mean±SD) | 29.6±11 | 25.9±4 | 0.061 |
| Hemoglobin level (g/dL) (mean±SD) | 14.2±1.1 | 14.3±0.9 | 0.869 |
| Leukocyte count (mean±SD) | 11.9±1.04 | 7.4±2.1 | 0.001 |
| CA-125 level (mean±SD) | 9.8±9.3 | 4.6±1.5 | 0.001 |
| *Student t-test. SD: standard deviation | | | |

**Table 2.** Distribution of pathological diagnosis of the cases

| | n | % |
|---|---|---|
| Simple appendicitis | 22 | 59.5 |
| Gangrenous appendicitis | 10 | 27 |
| Perforated appendicitis | 5 | 13.5 |

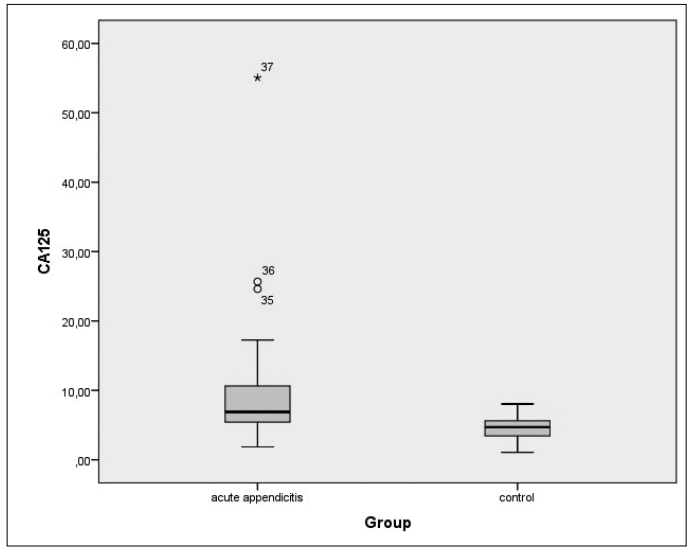


**Figure 1.** CA125 values according to group

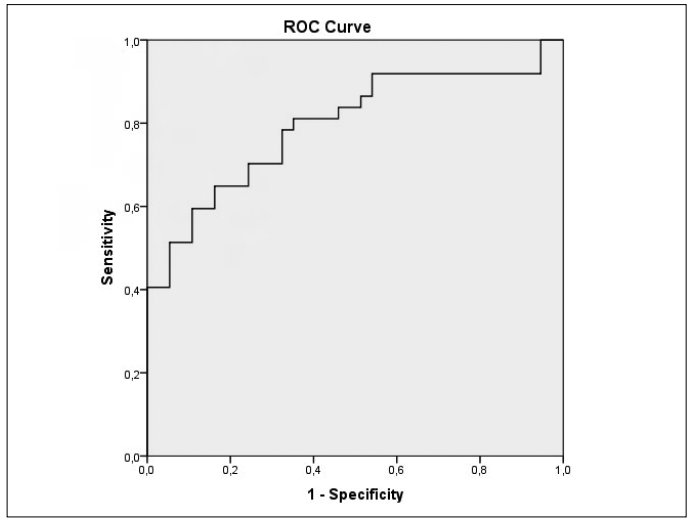


**Figure 2.** ROC curve for CA125 value for diagnosis of acute appendicitis

routinely used at emergency departments. Other inflammatory mediators like interleukins and procalcitonin are evaluated for diagnosis of AA (3, 4). However, in a meta-analysis they found no useful effect of several mediators on AA diagnosis (3).

The gold standard treatment for AA is appendectomy; however, recent literature shows that uncomplicated cases can be treated medically. There are several reports on the medical treatment of AA. A recent meta-analysis reported that medical treatment can be chosen in uncomplicated cases (16). In studies evaluating the antibiotic treatment of AA, the main debate is that the negative appendicitis rate is not known. Traditionally, the negative appendectomy rate is about 15%, which can decrease to 10% with the use of computed tomography (17). However, in trials with only antibiotic treatment, determination of the exact negative case rate is impossible. Therefore, there is a need for certain diagnosis of AA. The Alvarado score is a widely-used scoring system for the diagnosis of AA (18). However, the sensitivity of this scoring system is low in cases with low scores. In a study, the low modified Alvarado score was less sensitive compared with unstructured clinical judgment (19).

CA125 is glycoprotein mainly secreted from mesothelial cells. It is commonly used as a tumor marker for gynecological cancer. However, it secretion from peritoneal epithelium in case of inflammation is demonstrated by in vitro studies (9). According to Basaran (20), the main debate is thatCA125 secretion begins six hours after the onset of inflammation. In AA, both visceral and parietal peritoneum are affected. Therefore, theoretically, at the time of diagnosis, CA125 levels should be elevated. Berger et al. (10) evaluated the relation between AA and CA125. They reported that CA125 levels were higher in cases with AA than in cases without AA. Moreover, they reported that there is a positive correlation with disease severity. Similarly, Cetinkaya et al. (21) evaluated the relation between CA125 and perforated AA. They concluded that high levels of CA125 may show perforated cases. They reported the cutoff value for the diagnosis of complicated AA as 35 U/mL, with the sensitivity, specificity, and PPVs of 60%, 100%, and 100%, respectively. Recent study demonstrates that CA125 serum levels can help to diagnose AA patients.

### Study limitations

The main limitation of the current study is that only male cases were included. However, it is very difficult to differentiate the fluctuations during the menstrual cycles of female cases. Large-scale studies may answer this question by analyzing the cases at the same period of the menstrual cycle.

## Conclusion

In this study, we did not evaluate the correlation with the disease severity. However, we consider that CA125 levels can be used as a marker of AA in cases with clinical doubt.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Selçuk University School of Medicine (Date: December 24, 2013; number: 2013/378).

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

**Peer-review:** Externally peer-reviewed.

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

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

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# Evaluation of the VKORC 1 and CYP2C9 Gene Polymorphisms and Their Effects on the Emergency Complications in the Patients Using Warfarin

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## Abstract

**Aim:** We aimed to evaluate the effects of genetic polymorphisms on the frequency of application to the emergency service and on the complications with use of warfarin in this study.

**Materials and Methods:** Seventy patients were included in the study. Two groups were composed: one group of 40 patients who used warfarin and with international normalized ratios (INRs) ≥3.5 IU and a second group of 30 control group patients with normal INR levels. Blood samples were examined through the warfarin dosage sensitivity test.

**Results:** VKORC 1 heterozygote type AG was the most frequently seen allele in 17 of the haplotype patients (42.5%), in 12 of the control group patients (40%), in 21 of the CYP2C9 *1/*1 patients (52.5%), and in 17 of the CYP2C9 *1/*1 control group patients. No statistically significant difference was identified between the groups (p>0.05). No statistically significant relationship was established as regards the frequency of emergency service visits and bleeding complications with CYP2C9 and VKORC 1 genes.

**Conclusion:** The most common haplotypes VKORC 1 heterozygote type AG and CYP2C9 *1/*1. No relationship was identified between INR levels and VKORC 1 and CYP2C9 haplotypes. These genes have no effect on bleeding and frequent applications of emergency service.

**Keywords:** Warfarin, gene polymorphism, emergency service, VKORC 1, CYP2C9

## Introduction

Warfarin is a most commonly drug used for the prophylaxis and treatment of venous and arterial thromboembolism. It is now known that genetic factors also play a part in the effect mechanism of warfarin (1). So far, nearly 30 genes have been reported concerning the pharmacokinetics of warfarin. Cytochrome P450 2C9 (CYP2C9), vitamin K epoxide reductase complex subunit 1 gene (VKORC1) genes, and their polymorphisms are the ones that have the closest relationship with warfarin (2-4). VKORC1 is a gene and its polymorphism belonging to vitamin K epoxide reductase enzyme enabling vitamin K to be formed from reduced vitamin K epoxide. It has recently been reported that there are a lack of a resistance to warfarin (2), whereas the most common mutations that affect the dosage regulation of warfarin in VKORC 1 genotypes are 1173, 3730, and -1639 single nucleotide polymorphisms (5-8). Another important genetic factor is CYP2C9, a liver enzyme that plays a role in the oxidative metabolism of many other drugs as well as warfarin, and a series of gene polymorphisms were identified in the CYP2C9 gene area (3, 4). It has been demonstrated that these polymorphisms lead to difficulty in achieving a stable dosage in patients using warfarin, a decrease in the dosage requirement for warfarin, and a high risk of bleeding at an earlier period of drug use (8). The American Food and Drug Administration recommended that the starting dosage of warfarin should be regulated in accordance with the CYP2C9 and VKORC1 genotypes (5). This study aims to evaluate whether the patients who applied to the emergency unit with supratherapeutic international normalized ratio (INR) levels after using warfarin were different as regards CYP2C9 and VKORC1 genetic polymorphisms than the control group patients with therapeutic INR levels. I addition, this study attempts to reveal the effects of CYP2C9 and VKORC1 genetic polymorphisms on warfarin dosages, the frequency of application to the emergency unit, and the complications that develop due to use of warfarin.

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## Materials and Methods

### Study design

The study was a prospective clinical study. After obtaining the approval of the local ethical board, we conducted the study at the Emergency Service of Keçiören Training and Research Hospital between December 15, 2015, and January 1, 2016. Seventy patients who applied to our emergency department for any complaints or for INR control were included the study. Forty patients who had been using warfarin for more than one month and who had INR levels of 3.5 or more were included consecutively in the case group. A control group consisting of 30 patients was included for comparison. The control group was composed of patients who had applied to the emergency service for INR control and who did not have any warfarin overdose (their INR levels were below 3.5). After the patients and their relatives were informed about the situation, the patients for whom confirmation was obtained were taken into the study.

### The excluded criteria

Patients who were under the age of 18, who had been using warfarin for less than one month, who were using amiodarone, furosemide, heparin, quinolone, metronidazole, omeprazole, sulfonylureas, phenytoin, and tricyclic anti-depressants, and who had an infection were excluded from the study.

### Analysis of blood samples

Three milliliters of blood were taken into tubes with sterile ethylenediamine tetraacetic acid. Isolation of genomic DNA was carried out from the blood samples, following an algorithm, and the distribution of CYP2C9 and VKORC1 alleles between the patients and their relationship with the other variables were examined.

### CYP2C9 and VKORC1 alleles

In our study, we used the PGX-Thrombo Strip Assay (Vienna, Austria) test for laboratory and examined VKORC1-1639 G>A mutant and wild type, CYP2C9 1075 A>C mutant and wild type, and CYP2C9 430 C>T mutant and wild type alleles.

The presence of polymorphism in the patients is demonstrated in Table 1.

**Table 1.** Types of polymorphism

| | Wild type line | Mutant line | Genotype |
|---|---|---|---|
| Normal | Positive | Negative | Normal |
| Heterozygote | Positive | Positive | Heterozygote |
| Homozygote | Negative | Positive | Homozygote mutant |

### VKORC 1 genotypes

-1639 G>A, expressed as VKORC 1 AA, is made up of homozygote mutant genotypes,

-1639 G>A, expressed as VKORC 1 AG, is made up of heterozygote genotypes, and

-1639 G>A, expressed as VKORC 1 GG, is made up of homozygote normal (wild) genotypes.

### CYP2C9 genotypes

CYP2C9 alleles formed through the mutations of 430 C>T and 1075 A>C are shown in Figure 1 as *1 (wild type), *2 and *3. Homozygotes and heterozygotes are shown as *1/*1, *1/*2, *1/* 3, *2 /* 2, and *2/*3.

### Statistical analysis

The statistical analysis of the study was carried out with the IBM Statistical Package for the Social Sciences (IBM SPSS Statistics, Armonk, NY, USA) version 20.0 package program. In order to evaluate the compatibility of the distribution of alleles and haplotypes with the normal distribution, the Shapiro–Wilk test was employed. For the data that were compatible with the normal distribution, Student t-test was used. For the data that were not compatible, the Mann-Whitney U test was utilized. Descriptive statistics were shown in the form of mean ± standard deviation or median (minimum to maximum) for interrupted and continuous numeric variables. Categorical variables were shown in the form of case number and percentage (%). Pearson's X2 test was used for the evaluation of categorical variables. Logistic regression analysis was conducted to compare each polymorphism and the average warfarine dosage of the patients.

## Results

Seventy patients who aged 18–80 were taken into our study. The demographic features of the patients are shown in Table 2.

Vitamin K epoxide reductase complex subunit 1 heterozygote type AG haplotype was the most commonly seen allele identified in 17 patients in the patient group (42.5%) and in 12 patients in the control group (40%), whereas CYP2C9 *1/*1 was the most commonly seen allele identified in 21 patients in the patient group (52.5%) and CYP2C9 *1/*1 was the most commonly seen allele found in 17 patients in the control group (56.7%). No statistical difference was detected between the groups (p>0.05) (Table 3).

In terms of INR levels of the patient group, no statistical difference was found between VKORC 1 and CYP2C9 haplotypes (p=0.305 and p=0.088, respectively), whereas a significant difference was found on weekly warfarin dosages of VKORC 1 homozygote normal GG and CYP2C9 *1/*1 homozygote normal (wild) carriers (p=0.02 and p=0.034, respectively) (Table 4).

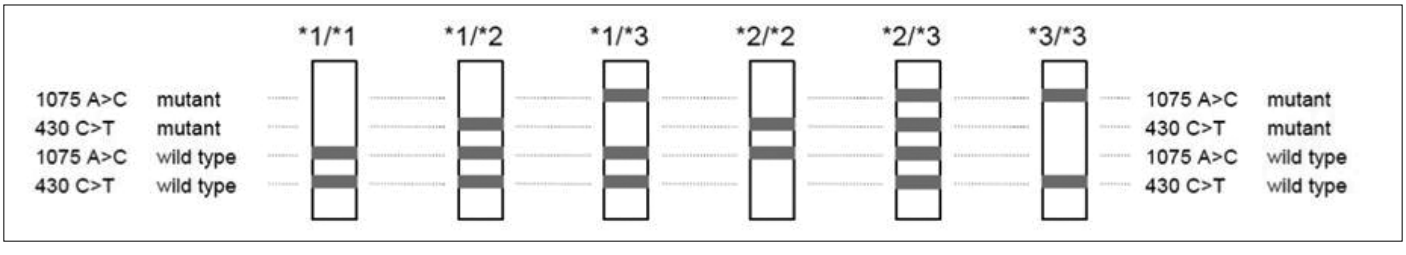


**Figure 1 .** CYP2C9 genotypes

**Table 2.** Clinical characteristics of study

| | Case, n (%) | Control, n (%) | p |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Female | 31 (77.5) | 22 (73.3) | 0.687 |
| Male | 9 (22.5) | 8 (26.7) | |
| **Age median (IQR 25-75)** | 76 (50-80) | 68.5 (50-80) | 0.012 |
| **Comorbidity, n (%)** | | | |
| Diabetes mellitus | 8 (20) | 10 (33.3) | 0.207 |
| Hypertension | 26 (65) | 22 (73.3) | 0.457 |
| Coronary artery disease | 16 (40) | 14 (46.7) | 0.577 |
| Other | 19 (47.5) | 10 (33.3) | 0.234 |
| **Indication for warfarin therapy, n (%)** | | | |
| Atrial fibrillation | 17 (42.5) | 9 (30) | 0.010 |
| Heart valve replacement | 9 (22.5) | 17 (56.7) | |
| Thromboembolism | 14 (35) | 4 (13.3) | |
| **Bleeding, n (%)** | 17(42.5) | 1 (3.3) | - |
| **Bleeding field, n (%)** | | | |
| Gastrointestinal bleeding | 5 (12.5) | | |
| Hematuria | 2 (5) | | - |
| Epistaxis | 2 (5) | 1 (3.3) | |
| Skin | 2 (5) | | |
| Hemoptysis | 1 (2.5) | | |
| Other | 2 (5) | | |
| **The number of overdose in the last year (%)** | | | |
| 0 | - | 19 (63.3) | |
| 1 time | 25 (62.5) | 6 (20) | |
| 2 times | 11 (27.5) | 4 (13.3) | |
| 3 times and higher | 4 (4) | 1 (3.3) | <0.05 |

IQR: interquartile range

**Table 3.** Distribution of CYP2C9 and VKORC1 genotypes

| Genotype | | Frequency, n (%) case | Frequency, n (%) control | p |
|---|---|---|---|---|
| VKORC 1 | AA | 14 (35) | 9 (30) | |
| | AG | 17 (42.5) | 12 (40) | |
| | GG | 9 (22.5) | 9 (30) | 0.53 |
| CYP2C9 | *1 / *1 | 21 (52.5) | 17 (56.7) | |
| | Others | 19 (47.5) | 13 (53.7) | 0.630 |

VKORC1: vitamin K epoxide reductase complex subunit 1 gene; CYP2C9: cytochrome P450 2C9; Others: CYP2C9 *1 / *2, *1 / *3, *2 / *2, *2 / *3, *3 / *3 haplotypes

**Table 4.** The relationship with the weekly warfarin dose and INR of genotypes in case groups

| | INR median (min-max) | | Weekly warfarin dose median (min-max) | |
|---|---|---|---|---|
| **Genotypes** | **Case** | **p** | **Case** | **p** |
| **VKORC 1** | | | | |
| AA | 8.36 (3.83–15.63) | 0.3 | 26.2 (17.5–35) | 0.02 |
| AG | 7.76 (4.03–15) | | 30 (13.75–35) 35 (17.5-45) | |
| GG | 4.82 (3.62–13.48) | | | |
| **CYP2C9** | | | | |
| *1/*1 | 8.77 (3.62–15) | 0.08 | 35 (17.5–40) | |
| Others | 2.32 (3.83–15.63) | | 27,5 (17.5–40) | 0.03 |

VKORC1: vitamin K epoxide reductase complex subunit 1 gene; CYP2C9: cytochrome P450 2C9; INR: international normalized ratio; Others: CYP2C9 *1/*2, *1/*3, *2/*2, *2/*3, *3/*3 haplotypes

When the number of visits by the patients to the emergency service was evaluated, it was shown that patients from the case group had more frequest admission to emergency service. (p=0.001) (Table 2). In terms of the frequency of visits to the emergency service, no statistical difference was found either for CYP2C9 or for VKORC 1 (Table 5).

Gastrointestinal bleeding was the most frequently observed form of bleeding . Complications due to bleeding were present in patient group, whereas it was observed in 17 patients in the case group (42.5%). No statistical difference was established between CYP2C9 and VKORC 1 haplotypes in terms of complications due to bleeding (p>0.05 and p=0.576, respectively) (Table 6).

Finally, when we evaluated to association between the average warfarin dosage of the patients and the gene polymorphism by logistic regression analysis, we did not find any correlation (p=0.2).

## Discussion

In our study, in which we evaluated the effect of CYP2C9, VKORC1 genetic polymorphisms, warfarin dosages and complications, no difference was observed between the patient and control groups in terms of haplotypes in warfarin-using patients. Moreover, it was seen that carriers of VKORC 1 homozygote normal GG and CYP2C9 *1/*1 homozygote normal (wild) had a higher dosage requirement for warfarin compared with the other genotypes. No relationship was found between INR levels and VKORC 1 and CYP2C9 haplotypes. VKORC 1 and CYP2C9 had no effect on bleeding and frequent visits to the emergency services.

There are two points that require particular attention in patients using warfarin during the process of treatment: (1) specifying an effective and safe stable dosage in the first months of the treatment, during which bleeding is particularly frequent, and (2) regulating this continual dosage in accordance with any change in the diet, weight, any new disease or additional drugs. Recent studies have revealed that genetic factors should also evaluate, as well as these factors (9). So, far, nearly 30 genes have been reported in association with warfarin pharmacogenetics. CYP2C9 and VKORC1 genes are the genes with the highest association with warfarin (2-4).

**Table 5.** The relationship between recurrent admission due to warfarin overdose of VKORC1 and CYP2C9 genotypes

| | VKORC 1 | | | | CYP2C9 | | |
|---|---|---|---|---|---|---|---|
| **Recurrent admission** | **AA** | **AG** | **GG** | **p** | ***1/*1** | **Others** | **p** |
| None | 6 (8.6%) | 6 (8.6%) | 7 (10%) | | 12 (17.1%) | 7 (10%) | |
| 1 time | 8 (11.4%) | 14 (20%) | 9 (12.9%) | 0.268 | 17 (24.3%) | 14 (20%) | 0.52 |
| 2 and more | 9 (12.9%) | 9 (12.9%) | 2 (2.9%) | | 19 (12.9%) | 11 (15.7%) | |
| Total | 23 (32.9%) | 29 (41.4%) | 18 (25.7%) | | 38 (54.3%) | 32 (45.7%) | |

VKORC1: vitamin K epoxide reductase complex subunit 1 gene; CYP2C9: cytochrome P450 2C9; Others: CYP2C9 *1/*2, *1/*3, *2/*2, *2/*3, *3/*3 haplotypes

**Table 6.** The relationship between bleeding complications of VKORC1 and CYP2C9 genotypes

| | VKORC 1 | | | | CYP2C9 | | |
|---|---|---|---|---|---|---|---|
| **Bleeding** | **AA** | **AG** | **GG** | **p** | ***1/*1** | **Others** | **p** |
| Yes | 6 (8.6%) | 9 (12.9%) | 3 (4.3%) | | 10 (14.3%) | 8 (11.4%) | |
| No | 17 (24.3%) | 20 (28.6%) | 15 (21.4%) | 0.57 | 28 (40%) | 24 (34.3%) | >0.05 |
| Total | 23 (32.9%) | 29 (41.4%) | 18 (25.7%) | | 38 (54.3%) | 32 (45.7%) | |

VKORC1: vitamin K epoxide reductase complex subunit 1 gene; CYP2C9: cytochrome P4502C9; Others: CYP2C9 *1/*2, *1/*3, *2/*2, *2/*3, *3/*3 haplotypes

The prevalence of CYP2C9 and VKORC1 alleles varies with ethnic groups. In our study, we found that CYP2C9 *1/*1 haplotype was at a rate of 54.3%, and we identified it more commonly than we identified the other five haplotypes. While CYP2C9 *5 and *6 alleles were more prevalent in African society, the prevalence of CYP2C9 *2 and CYP2C9 *3 was found to be lower among Chinese and Malaysian people (10). There is considerable research in the literature demonstrating that genetic polymorphisms of CYP2C9 *2 and CYP2C9 *3 reduce the dosage requirement of warfarin (11-13). In Sanderson's study, CYP2C9 *2 genetic polymorphism reduced the dosage requirement by 17%, while CYP2C9 *3 genetic polymorphism reduced the dosage requirement by 37% (11). Similarly in the study by Lindh et al. (12) CYP2C9 *1/*1 carriers had a reduced dosage requirement compared with the other carriers (12). Also in our study, when CYP2C9 *1/*1 (homozygote normal) carriers were compared with the other carriers, no significant difference was observed as regards warfarin dosage requirement, as has been demonstrated in the literature.

The VKORC 1 allele most frequently seen in our study was heterozygote type AG haplotype, but in VKORC 1 genotypes, the most common mutation that affected the dosage regulation were 1173, 3730, and −1639 single nucleotide polymorphisms (5-7). Among Japanese people, while the ratio of VKORC1 -1639 G/G homozygote normal was extremely high (79.4%), the ratio of -1639 A/A homozygote mutant was negligibly low (0.8%) (6). In a study conducted by Gan et al. (14) revealed that VKORC 1 genetic polymorphism was quite common among Chinese and Malaysian people, but it had a low ratio among Indian people. These polymorphisms, which were identified in the VKORC 1 gene, could change the dosage requirement for warfarin. Özer et al. (13), stated that VKORC1 -1639 G > A polymorphisms had the most important role. Similarly, in a study by Gan et al. demonstrated that patients with the GG genotype in the gene area of VKORC1 -1639 G > A had the highest dosage requirement for warfarin, patients with the AG genotype had a moderate dosage requirement for warfarin, and patients with the AA genotype had the lowest dosage requirement for warfarin (14).

Also in our study, a statistically significant difference was detected between haplotypes as regards warfarin dosage requirement both in the case group, in which the effect of overdose was seen at the time of the application, and in the control group, in which the ideal dosage was supposedly reached and no effect of overdose was seen. It was determined that while a higher dosage of warfarin was needed for VKORC 1 GG carriers, a lower dosage of warfarin was required for VKORC 1 AA carriers.

Warfarin is used in different indications and in increasing amounts today increases the likelihood of its side effects as well as its benefits (15). The most serious side effect resulting from an overdose of warfarin treatment is bleeding. When we evaluated the role of CYP2C9 and VKORC1 genetic polymorphisms in frequent applications to the emergency service and bleeding complications, we were unable to detect any effects of CYP2C9 and VKORC 1 haplotypes in terms of bleeding and frequent applications to the emergency service. We think that this may stem from the low number of the patients in our study.

### Study limitations

Our study is a single-center study. The number of cases is low. Another limitation of our study is the fact that there were age differences between the patients in the patient and control groups. Apart from genetic factors, there are a number of factors that have an effect on the pharmacogenetics of warfarin. Among them, age is the leading factor. In our study, the difference in ages between the groups, as well as genetic polymorphism, might have had an effect on the weekly warfarin dosage that the patients used.

## Conclusion

In this study, we could not clarify the effects of genetic polymorphisms on warfarin overdose and associated complications in emergency services. This may have to do with the low number of patients in our study. Further studies that include more patients and through

which better results could be obtained with respect to cost and efficiency are required.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Keçiören Training and Research Hospital.

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

**Peer-review:** Externally peer-reviewed.

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# Comparison of the AIMS-65 Score with the Glasgow-Blatchford Score in Upper Gastrointestinal Bleed in the Emergency Department

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## Abstract

**Aim:** Upper gastrointestinal (UGI) bleed can be a life-threatening condition commonly seen in the emergency department (ED). Hence, to efficiently allot resources, optimize care, and ascertain the disposition of the patient, it is important to determine the severity of UGI bleeding. The objective of the study is to compare patients presenting with UGI bleeding with both the AIMS-65 and GBS to determine most appropriate score in prognosticating clinical outcomes and to identify high-risk patients needing transfusion of blood, endoscopic intervention, and admission to an intensive care unit (ICU) from the ED.

**Materials and Methods:** A prospective, observational study of patients presenting with an UGI bleed from April 2014 to June 2015. All patients above 18 years of age presenting to the ED with hematemesis, melena, or having blood on nasogastric aspirate are enrolled into the study. Patients aged less than 18 years with hemoptysis, hematochezia, or traumatic oral bleeding were excluded. The AIMS-65 and GBS were calculated for all patients and correlated with the duration of their stay in the hospital, mortality, the need for blood transfusion and endoscopy.

**Results:** Of the 138 UGI bleeding patients, 37% had esophageal varices and 23% had peptic ulcer disease. The GBS was better than the AIMS-65 in predicting the need for blood transfusion. Compared with the GBS, the AIMS-65 score was statistically significant in prognosticating mortality in-hospital and the patient's disposition to the ward or an intensive care unit.

**Conclusion:** The AIMS-65 score is a simple, appropriate, non-endoscopic risk score that can be employed in patients with acute UGI bleeding, aiding in triage, early decision-making, and proper disposition from the ED.

**Keywords:** Upper gastrointestinal bleed, gastrointestinal hemorrhage, UGI bleed, Glasgow-Blatchford Score, AIMS-65, endoscopic intervention, ICU Care, blood transfusion, disposition from ED, emergency department

## Introduction

Upper gastrointestinal (UGI) bleed is a common life-threatening condition seen in the emergency department (ED) (1-3). A careful assessment is mandatory to determine the risk of re-bleeding or death (3). The incidence of UGI bleeding is 50–170 per 100,000 people per year (4). The American College of Gastroenterology practice guideline (5) advises that risk assessment should be done to aid the clinician in making the all-important decision regarding the disposition of the patient (6).

Not all UGI bleeds require an emergency intervention (7, 8). Even though patients with UGI bleed are admitted and managed with inpatient care and endoscopy, this approach is controversial due to the use of a substantial number of resources. Various risk scoring methods for UGI bleeding have been generated and used to predict the need for intervention or survival and to develop a standard management strategy (7, 9-14). An endoscopy-based triage is suggested to reduce cost and stay in hospitals (15), but it is rarely practiced due to the regular unavailability of emergency endoscopy. In such places, a scoring system dependent on clinical features would be desirable for the ED physician (16, 17).

The Glasgow-Blatchford risk score (11) (GBS) and the pre- and post-endoscopic Rockall score (7) have been compared to predict clinical outcomes such as 30-day mortality, the need for hospital-based intervention, blood transfusion, the likelihood of re-bleeding, surgical intervention and, the suitability for early discharge. Despite its limitations, the GBS (11, 18) is still comparable or better than the Rockall score (19-23), and encouraging GBS use in routine risk stratification.

The AIMS-65 score was derived from a comprehensive database and validated to predict inpatient mortality (14). The AIMS-65 is sim-

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pler, as it is not weighted and does not require endoscopic findings, thus making it easier to remember and use AIMS-65 score (24). The AIMS-65 does not rely on medical history. Only laboratory investigations commonly performed in an ED and the mental health status of the patient are required.

The objective of this study is to compare patients presenting with UGI bleeding with both the AIMS-65 and GBS to determine the most appropriate score used in prognosticating clinical outcomes and to identify high-risk patients needing transfusion of blood, endoscopic intervention, and admission to an intensive care unit (ICU) from the ED.

## Materials and Methods

A prospective, observational study of all patients presenting with UGI bleeding, registered in the ED of a tertiary care university teaching hospital in Chennai, India, which has an annual input of 30,000 patients. The study was conducted over a period of 15 months from April 2014 to June 2015. All patients above the age of 18, presenting to the ED with complaints of hematemesis, melena or having blood on nasogastric aspirate were enrolled in the study.

Patients aged less than 18 years with a history of hemoptysis, hematochezia, and traumatic oral bleeding were excluded.

### Methodology

Once a patient was identified as having UGI bleeding, the treating emergency physician would enter the details of the patients into a preformatted questionnaire. The patient's demographic data, comorbid illness, Glasgow Coma Scale (GCS) score, previous history of surgery/bleeding, history of melena, syncope, vital signs, and the initial investigation values were entered in the questionnaire. The disposition and the clinical outcomes of the patients were also recorded.

As part of the acute care and resuscitation, all UGI bleeding patients received intravenous proton pump inhibitor therapy as a standardized treatment, and patients with variceal hemorrhage received vasoactive therapy with octreotide or somatostatin. A medical gastroenterologist admitted these patients and decided the need for endoscopy, the timing of endoscopy, and the disposition to the ICU or ward.

Patients who were admitted to the ICU or required blood transfusion were considered high-risk patients. All causes of death during hospitalization were considered mortality, while morbidity was related to the number of days of hospitalization. Only the patient data recorded at the time of presentation to the ED were utilized for the study analysis.

Both the AIMS-65 and GBS were calculated for all patients included in the study, based on the original study criteria (11, 14). The indication for blood transfusion was defined as 30–40% blood loss (1500–2000 mL). The admission criteria was defined as (a) age ≥60 years, (b) witnessed hematemesis or hematochezia (suspected continued bleeding), (c) hemodynamic disturbance (SBP <100 mmHg or heart rate >100 bpm), and (d) patients with a known liver disease or varices. The exact study definition for the need of endoscopy, admission to the ICU, and the time for endoscopy was not defined as it was at the discretion of the treating gastroenterologist.

The GBS is derived using the patient's hemoglobin and blood urea nitrogen levels; vital signs like systolic blood pressure and heart rate; and history of syncope, melena, cardiac failure, or hepatic disease (11). The score ranges from 0 to a maximum of 23 (Table 1). The GBS had previously been validated with a suitable cutoff of less than 2 for low-risk patients (8, 25, 26).

The AIMS-65 score is derived using the patient's age (>65 years), blood pressure, GCS score, INR, and albumin levels (14). Each criterion is given a point, and the score ranged from 0 to a maximum of 5 (Table 2). Only a few validation studies have previously been done for the AIMS-65.

### Statistical analysis

The data collected in the preformatted questionnaire were entered into a spreadsheet (Microsoft Office Excel 2007; Microsoft Corporation, Redmond, WA, USA). For categorical variables, descriptive analysis like frequency and percentage were calculated. Moreover, for continuous data, the mean and standard deviation were derived. The sensitivity, specificity, positive predictive value (PPV), and neg-

**Table 1.** Glasgow-Blatchford score for assessing the severity of UGI bleeding

| **Admission Risk Marker** | | **Score** |
|---|---|---|
| Blood Urea (mmol/L) | ≤6.5-7.9 | 2 |
| | 8-9.9 | 3 |
| | 10-24.9 | 4 |
| | ≥25 | 6 |
| Hemoglobin–Men (g/dL) | ≥12 | 1 |
| | 10-11.9 | 3 |
| | <10 | 6 |
| Hemoglobin–Women (g/dL) | ≥10 | 1 |
| | <10 | 6 |
| Systolic Blood Pressure (mmHg) | ≥100 | 1 |
| | 90-99 | 2 |
| | <90 | 3 |
| Other Markers | Pulse ≥100 | 1 |
| | Melena | 1 |
| | Syncope | 2 |
| | Liver Disease | 2 |
| | Heart Failure | 2 |

**Table 2.** The AIM65 score for assessing the severity of UGI bleeding

| **Feature** | **Score** |
|---|---|
| Albumin less than 3.0 g/dL (30 g/L) | 1 Point |
| INR greater than 1.5 | 1 Point |
| Altered mental status (Glasgow Coma score less than 14, disorientation, lethargy, stupor, or coma) | 1 Point |
| Systolic blood pressure of 90 mmHg or less | 1 Point |
| Age older than 65 years | 1 Point |
| Total Score: 0–5 | |

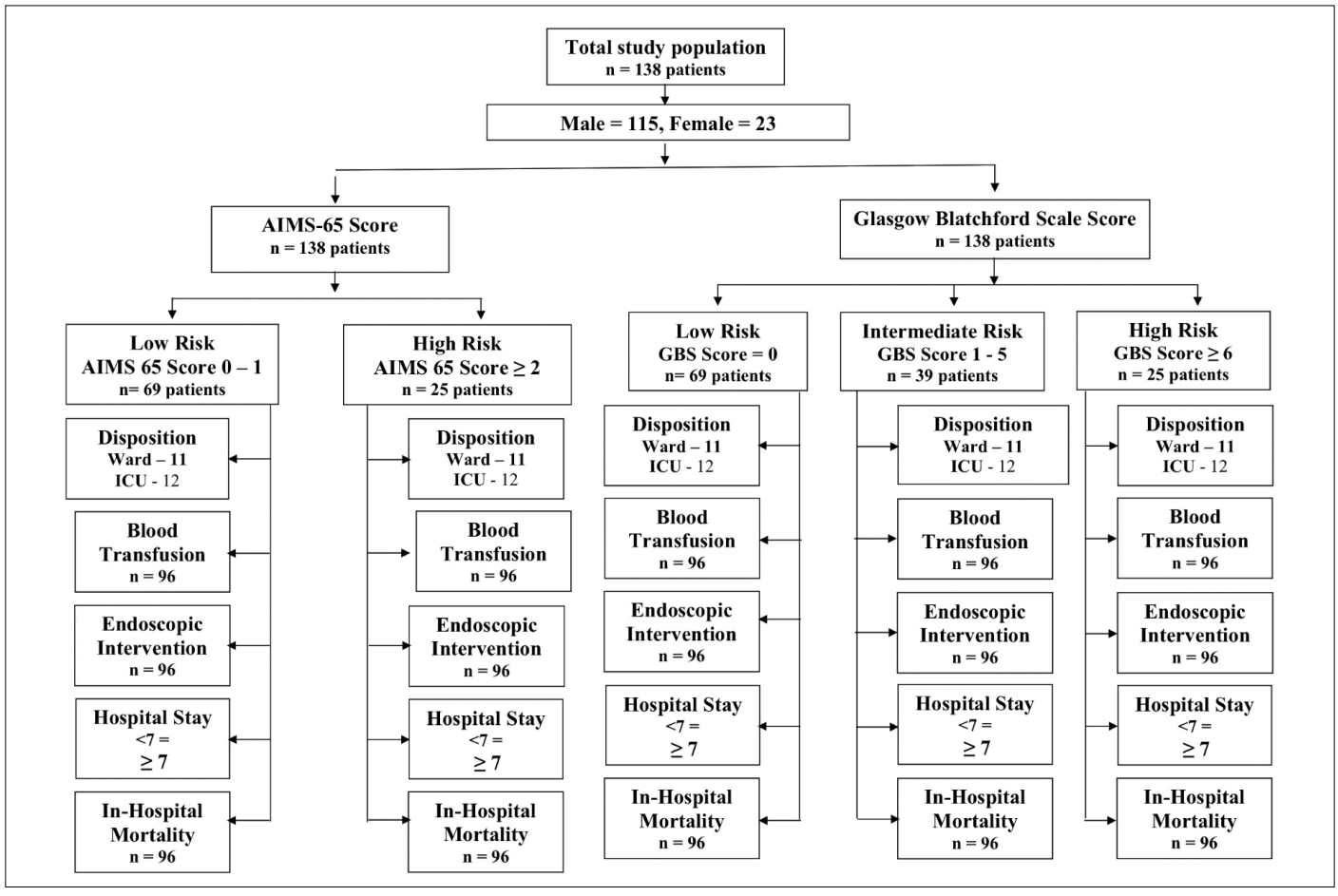


**Figure 1.** A flowchart Comparing AIMS-65 Vs GBS Scores against five outcomes

ative predictive value (NPV) were analyzed to assess the predictive accuracy of the study outcome using the area under the receiver-operating characteristic (ROC) curve. A p-value of 0.05 was considered as a significant level. Statistical analysis was done using statistical software (IBM SPSS version 23.0; Armonk, NY, USA). This study was approved by the institutional ethics committee, and a written consent was taken from each patient or his/her attendant in both English and his/her mother tongue.

## Results

A total of 138 patients were included in the study (Figure 1). Eighty-three percent of the patients in the study were male, with 42% of the patients aged between 61 and 80 years, with ages ranging from 18 to 89 years. Systolic blood pressure <120 mmHg was observed in 70% of the patients, diastolic blood pressure <80 mmHg was observed in 74% of the patients, and tachycardia was present in 62% of the patients. Among the 138 patients with UGI bleeding, 89% presented with a history of melena, 26% presented with the history of syncope, and 15.2% had associated hepatic diseases. Seventy-two percent of patients presented with a GCS of 15. Abnormal BUN levels were observed in 58% of the patients, 61.6% had abnormal albumin levels, and 71% had elevated INRs of more than 1.2 (Table 3). The data of performance (sensitivity and specificity) were calculated in our study with a cut off score of 1.5 for the AIMS-65 score and 8.5 for the GBS.

It was observed that 51% of the patients (71/138) received a blood transfusion (Table 4). The AIMS-65 score predicted that 42 patients required a blood transfusion, whereas the GBS predicted that 43 patients needed blood transfusions (p=0.001). The GBS is the optimal choice, even though both the AIMS-65 score and the GBS have an acceptable prediction rate for classifying a patient's need for blood transfusion (Figure 2).

In our study, 66.7% of patients (92/138) were stable enough to be admitted to the ward, whereas 33.3% required admission to the ICU (46/138). A comparison of both scoring systems was made to predict the need for admission to the ICU (Figure 3). The AIMS-65 score predicted that 31 patients required admission to the ICU; however, the GBS predicted that only 26 patients required admission to the ICU (p=0.001) (Table 5, 6). The in-hospital mortality was 13.2% (18 patients). The AIMS-65 and GBS were compared to predict mortality (Figure 4). The AIMS-65 score with a high predictive power (AUC=0.672; p=0.019) is significantly better with a sensitivity 72% and NPV of 90%. However, the GBS (AUC=0.601; p=0.166) had a sensitivity of 56% and NPV 88%. We thus suggest that the AIMS-65 is the optimal choice for predicting the need for admission to the ICU and in-hospital mortality.

Endoscopy was performed for 79% of the patients (109/138), 32.1% (35/109) of whom required endoscopic intervention such as banding, endotherapy, and adrenaline injection. The AIMS-65 score predicted that 20 patients required intervention during endoscopy,

**Table 3.** Demographic and clinical characteristic features of patients presenting with UGI bleeding

| No | Feature | | Frequency (n=138) | % |
|---|---|---|---|---|
| 1. | Age | Up to 40 years | 22 | 15.9 |
| | | 41–60 years | 47 | 34.1 |
| | | 61–80 years | 58 | 42 |
| | | >80 years | 11 | 8 |
| 2. | Gender | Male | 115 | 83.3 |
| | | Female | 23 | 16.7 |
| 3. | Systolic blood pressure | <120 mmHg | 96 | 69.6 |
| | | >120 mmHg | 42 | 30.4 |
| 4. | Diastolic blood pressure | <80 mmHg | 102 | 73.9 |
| | | >80 mmHg | 36 | 26.1 |
| 5. | Heart rate (beats per minute [bpm]) | HR >100 bpm | 86 | 62.3 |
| | | HR <100 bpm | 52 | 37.7 |
| 6. | Melena | Positive | 123 | 89.1 |
| | | Negative | 15 | 10.9 |
| 7. | Syncope | Positive | 36 | 26.1 |
| | | Negative | 102 | 73.9 |
| 8. | Hepatic disease | Positive | 21 | 15.2 |
| | | Negative | 117 | 84.8 |
| 9. | Cardiac disease | Positive | 13 | 9.4 |
| | | Negative | 125 | 90.6 |
| 10. | Glasgow Coma Scale (GCS) Score | 8 or less | 5 | 3.6 |
| | | 9 to 14 | 33 | 23.9 |
| | | 15 | 100 | 72.5 |
| 11. | Hemoglobin (Hb) | <8 | 26 | 18.8 |
| | | 8–10 | 74 | 53.6 |
| | | 10.1–12 | 25 | 18.1 |
| | | >12 | 13 | 9.4 |
| 12. | Blood Urea Bitrogen (BUN) level | Normal | 58 | 42 |
| | | Abnormal | 80 | 58 |
| 13. | INR | Normal | 40 | 29 |
| | | Elevated | 98 | 71 |
| 14. | Albumin | Normal | 53 | 38.4 |
| | | Abnormal | 85 | 61.6 |

but the GBS predicted that 17 patients required intervention during endoscopy (Figure 5). In our study, 73.9% had less than a seven-day stay at the hospital, and 26.1% stayed more than seven days. The AIMS-65 and GBS were used to predict the length of hospital stay (Figure 6). The AIMS-65 score predicted that 18 patients required more than seven days of hospital stay compared with the GBS of 14 patients. Neither score was statistically significant (p=0.277 and p=0.474, respectively).

## Discussion

A few EDs utilize risk stratification tools for managing UGI bleeds, and no standard scoring system has been adopted, even though it has been recommended in many guidelines and consensus statements. The risk stratification scores should be simple, and accurate. They should also be easy to remember, calculate, and apply at the bedside by using clinical data obtained from the patient at presen-

**Table 4.** Investigation and outcomes in patients presenting with UGI bleeding

| No | Feature | | Frequency (n=138) | % |
|---|---|---|---|---|
| 1. | Endoscopy performed | Yes | 109 | 79 |
| | | No | 29 | 21 |
| 2. | Endoscopic findings | Esophageal varices | 42 | 37 |
| | | Gastritis | 18 | 16 |
| | | Gastric ulcer | 13 | 11 |
| | | Esophagitis | 12 | 11 |
| | | Duodenal ulcer | 10 | 9 |
| | | Duodenitis | 6 | 5 |
| | | Esophageal ulcers | 4 | 3 |
| | | Other | 9 | 8 |
| 3. | Endoscopic intervention | Yes | 35 | 25.4 |
| | | No | 103 | 74.6 |
| 4. | Endoscopic intervention | Banding | 30 | 85.7 |
| | | Endotherapy | 2 | 5.71 |
| | | Adrenaline injection | 3 | 8.57 |
| 5. | Blood transfusion | No | 67 | 48.6 |
| | | Yes | 71 | 51.4 |
| 6. | Disposition | Ward | 92 | 66.7 |
| | | ICU | 46 | 33.3 |
| 7. | Days of stay in hospital | ≤7 days | 102 | 73.9 |
| | | > days | 36 | 26.1 |
| 8. | Mortality | Dead | 18 | 13 |
| | | Recovered | 120 | 87 |

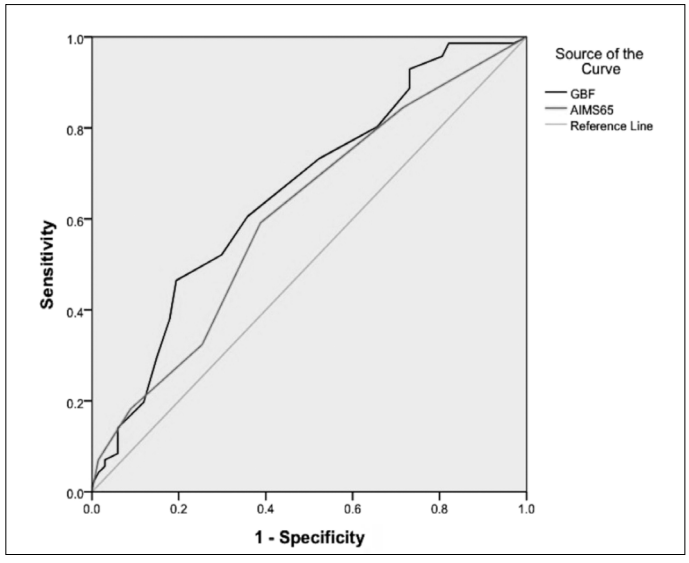


**Figure 2.** ROC comparing AIMS-65 and GBS scores predicting need for blood transfusion in UGI Bleeding patients

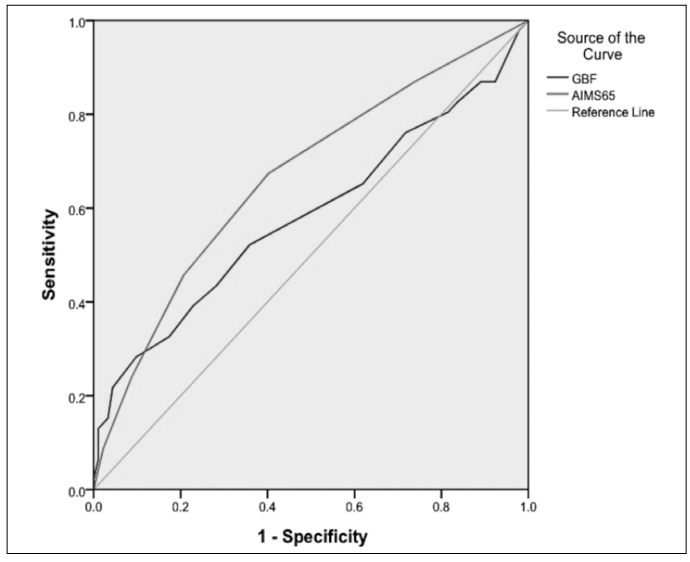


**Figure 3.** ROC comparing AIMS-65 and GBS scores predicting need for ICU in UGI Bleeding patients

**Table 5.** Comparison of sensitivity, specificity, PPV, and NPV for five different study outcome criteria between the AIMS-65 and GBS in UGI bleeding patients

| Study outcome criteria | | Accuracy (%) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Positive likelihood | Negative likelihood |
|---|---|---|---|---|---|---|---|---|
| Disposition | AIMS-65 | 63 | 67 | 60 | 46 | 79 | 1.7 | 0.6 |
| | GBS | 56 | 56 | 55 | 39 | 72 | 1.3 | 0.8 |
| Blood transfusion | AIMS-65 | 60 | 59 | 61 | 62 | 58 | 1.5 | 0.7 |
| | GBS | 63 | 61 | 64 | 64 | 61 | 1.7 | 0.6 |
| Endoscopic intervention | AIMS-65 | 55 | 57 | 53 | 29 | 79 | 1.2 | 0.8 |
| | GBS | 51 | 49 | 51 | 25 | 75 | 1 | 1 |
| Duration of hospital stay | AIMS-65 | 51 | 50 | 51 | 26 | 74 | 1 | 1 |
| | GBS | 46 | 40 | 48 | 21 | 70 | 0.8 | 1.2 |
| In-hospital mortality | AIMS-65 | 68 | 71 | 55 | 25 | 90 | 1.6 | 0.5 |
| | GBS | 57 | 67 | 55 | 24 | 88 | 1.5 | 0.6 |

PPV: positive predictive value; NPV: negative predictive value.

**Table 6.** Comparison of ROC analysis for five different study outcome criteria between the AIMS-65 and GBS in UGI bleeding patients

| Study outcome criteria | | AUC* | Std. error† | Asymp. sig.‡ | Asymptotic 95% confidence interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| ICU admission | AIMS-65 | 0.668 | 0.050 | 0.001§ | 0.570 | 0.765 |
| | GBS | 0.583 | 0.055 | 0.111 | 0.475 | 0.692 |
| Blood transfusion | AIMS-65 | 0.611 | 0.048 | 0.025§ | 0.517 | 0.705 |
| | GBS | 0.660 | 0.046 | 0.001§ | 0.569 | 0.751 |
| Endoscopic intervention | AIMS-65 | 0.533 | 0.056 | 0.560 | 0.423 | 0.643 |
| | GBS | 0.526 | 0.055 | 0.649 | 0.419 | 0.633 |
| Duration of hospital stay | AIMS-65 | 0.460 | 0.054 | 0.474 | 0.354 | 0.566 |
| | GBS | 0.439 | 0.054 | 0.277 | 0.333 | 0.545 |
| In-hospital mortality | AIMS-65 | 0.672 | 0.064 | 0.019§ | 0.547 | 0.798 |
| | GBS | 0.601 | 0.064 | 0.166 | 0.475 | 0.727 |

The cut-off points for the AIMS-65 and GBS were 1.5 and 8.5, respectively.

*AUC: area under the curve; †: standard error (under the nonparametric assumption); ‡: asymptotic significance (null hypothesis: true area = 0.5); §: statistically significant as $p<0.05$

tation to the ED and give independent predictive knowledge if they must be adopted widely (27, 28).

The most validated risk scores for UGI bleeding are the GBS and the Rockall score. However, these scores are poorly implemented by emergency physicians, as they have various limitations that include the need for endoscopic data, complex calculations, and weighting. The use of the AIMS-65 could help overcome the above limitations and help standardize the management of patients with UGI bleeding. The AIMS-65 is simple, acronym-based, easy to remember and calculate, highly accurate, and non-weighed and uses parameters easily and routinely collected in the ED (14). Like previous studies, this study validates the AIMS-65 score as an accurate risk stratification score in patients presenting with UGI bleeding.

Of the 138 patients included in this study, the majority of patients (42%) were aged between 61 to 80 years, with a median age of 67 years. In their studies, Cheng et al. (29) and Nakamura et al. (30) had a similar median age of 56 years and 66 years, respectively. In our study, 83% of males were affected with UGI bleeding compared with 17% of females. Similarly, Hyett et al. (5) and Nakamura et al. (30) also suggested that males presented to the ED with UGI bleeding more often than females did.

In our study, 15.2% of patients suffered from hepatic disease, and 9.4% of patients suffered from the cardiac disease. In contrast, in the retrospective study by LeCleire et al. in France (31), 21.9% of patients with UGI bleeding had hepatic disease. However, in the retrospective study by Dicu et al. in Romania, 58% of patients with UGI bleeding had cardiac disorders. Our study sample had fewer patients with hepatic disease than the above two studies, which can be a limitation in our findings. This difference between our study and the findings of Dicu et al. (3) and LeCleire et al. (31) may be due to the difference

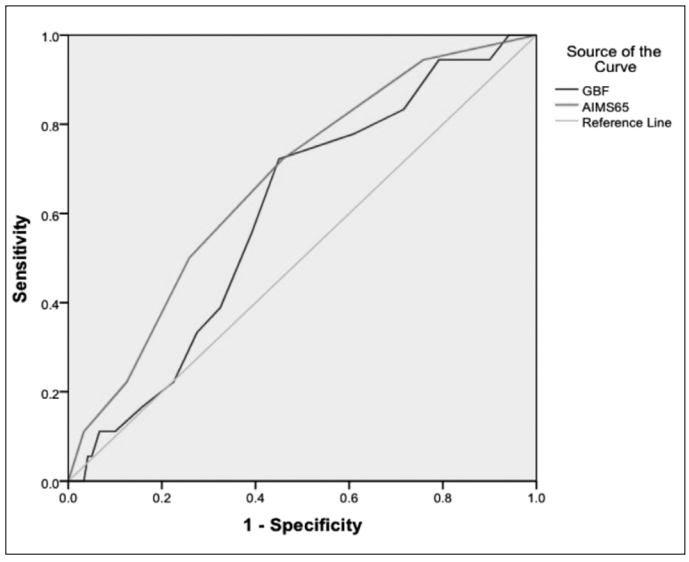


**Figure 4.** ROC comparing AIMS-65 and GBS scores predicting mortality in UGI Bleeding patients

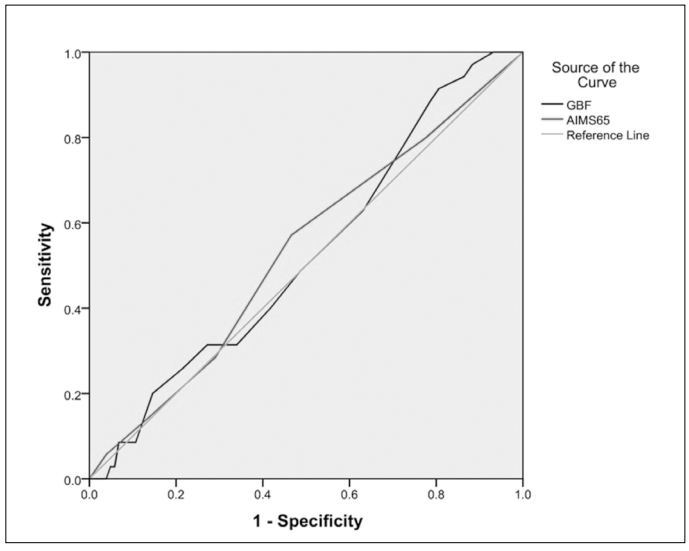


**Figure 5.** ROC comparing AIMS-65 and GBS scores predicting endoscopic intervention in UGI Bleeding patients

in the geographical location and food and lifestyle habits of the patients.

In our study, endoscopy was performed on 78.9% of patients, with a few patients being unstable or unwilling to undergo the procedure. Esophageal varices (37%) were the most common finding, followed by gastritis (16%), among those who had endoscopy for UGI bleeding. Similarly, Alema et al. (32), in their study of 224 patients, recorded that 40.6% suffered from esophageal varices, and Yaka et al. (17), in their study of 254 patients, showed that 16.5% of their patients had gastritis. However, Dicu et al. (3) also revealed that 41.4% of patients had gastric/duodenal ulcers and that only 27.9% had esophageal varices. Yaka et al. (17) observed that 34.6% of patients had gastric/duodenal ulcers and that only 9.4% had esophageal varices.

A total of 71 patients (51%) received blood transfusion either in the ED, the ICU, or wards. Previous studies have shown that for predicting the need for a blood transfusion, the GBS was better than

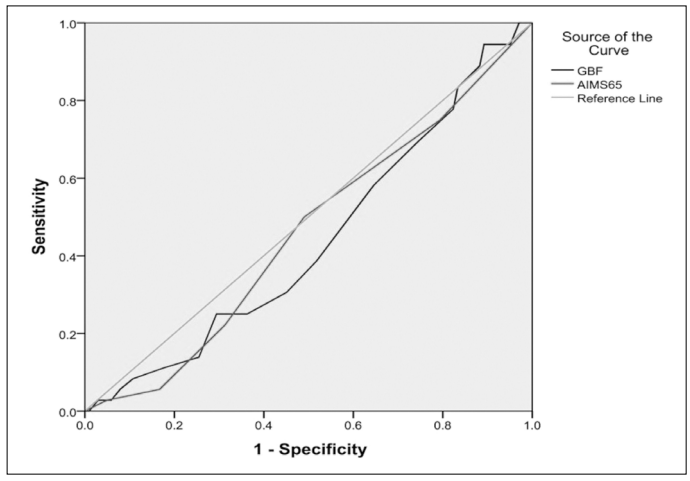


**Figure 6.** ROC comparing AIMS-65 and GBS scores predicting length of hospital stay in UGI Bleeding patients

other scores (3, 17, 20). A comparison of both scores for prognosticating the need for transfusion shows that the GBS has a higher predictive power than the AIMS-65 score (AUC=0.660 vs. AUC=0.611; p=0.001). The GBS is the optimal choice, even though both the scores have an acceptable prediction rate for classifying a patient's need for blood transfusion. Yaka et al. (17), in their study of 254 patients, also suggested that the GBS was better than the AIMS-65 in prognosticating the need for a blood transfusion (AUC=0.904 vs. AUC=0.796; p<0.001). Similarly, the results of our study also confirmed the superiority of the GBS. Because the levels of hemoglobin at presentation to the ED are included in the GBS, it is a superior predictor of need for blood transfusion.

We found that 92 patients (66.7%) were stable enough to be admitted to the ward, whereas 46 patients (33.3%) required admission to the ICU. A comparison of both scoring systems was made to predict the need for admission to the ICU. Our study established that the AIMS-65 is better than the GBS (AUC=0.668 vs. AUC=0.583; p=0.001) in predicting the need for admission to the ICU. Robertson et al. (24), in their study of 424 patients, also demonstrated that the AIMS-65 is better than the GBS in prognosticating the need for admission to the ICU (AUC=0.74 vs. AUC=0.70; p=0.001). Similarly, Hyett et al. (5) ascertained that the AIMS-65 is better than the GBS (AUC=0.69 vs. AUC=0.63; p=0.35) in predicting the need for admission to the ICU.

The in-hospital mortality was 18 patients (13.2%) in our study. It was observed that there were no deaths in patients with an AIMS-65 score of 0, and the number of fatalities rose with increasing AIMS-65 scores when both scores were compared to predict mortality. The AIMS-65 score with a high predictive power is significantly better than the GBS (AUC=0.672 vs. AUC=0.601; p=0.019). Similarly, Thandassery et al. (33) (AUC=0.74; p<0.001) and Hyett et al. (5) (AUC=0.93 vs AUC=0.68; p<0.001) observed that the AIMS-65 score was superior to the GBS in prognosticating in-hospital mortality.

Of the 109 patients (79%) who had an endoscopy, 35 required endoscopic intervention (32.1%) such as banding, endotherapy, and adrenaline injection. A comparison to prognosticate the need for intervention during endoscopy found the AIMS-65 has a superior specificity (52%), whereas the GBS has a higher sensitivity (57%) and a lower specificity 43%. Bryant et al. (34) suggested that the GBS predicted the need for endoscopic intervention in their study of 888 patients in which 80% of patients had an endoscopy and 40.3% re-

quired endoscopic therapy. Similarly, Yaka et al. (17), in their study of 254 patients, 83.1% of whom had an endoscopy and 19.3% of whom required endoscopic intervention, found that the GBS had a better prognosticating ability in ascertaining the need for an endoscopic intervention. The difference between the findings of Yaka et al. (17) and Bryant et al. (34) and those of our study may be explained by the fact that esophageal varices were the predominant etiology of UGI bleeding in our study population due to the different lifestyles of patients in our part of the world.

In our study, 102 patients (73.9%) had less than a seven-day stay at the hospital, and 36 patients (26.1%) stayed more than seven days. The AIMS-65 score has a superior predictive value than the GBS (AUC=0.460 vs. AUC=0.439) in predicting the length of hospital stay. However, in predicting the duration of hospital stay, there was no difference between the two scores (p=0.277 and p=0.474, respectively). Hyett et al. (5) found that both scores could prognosticate the duration of stay with higher scores predicting the longer length of stay (AUC = 0.15 [range 0.06–0.23] for the AIMS-65 and AUC = 0.17 [range 0.07–0.26] for the GBS). However, in predicting the outcomes, there was no difference between the AIMS-65 and GBS (p=0.151 and p=0.67, respectively). This difference may be due to the late presentation of patients or the physician's choice of management and timing of discharge.

Neither the AIMS-65 or GBS could predict the need for endoscopic intervention and the duration of hospital stay. This may be explained by the fact that our study population had fewer patients with chronic hepatic disease; the predominant etiology being esophageal varices. This can be attributed to the late presentation of patients to the ED due to lack of awareness. The need for endoscopy and the time for endoscopy were not defined as they were at the discretion of the treating gastroenterologist.

### Study limitations

There were a few limitations in this study. The AIMS-65 was originally designed to predict mortality, whereas the GBS aimed to predict the need for emergent endoscopy and blood transfusion. Evaluating both scores on different outcomes is one of the major limitations. Another limitation is that there were fewer chronic hepatic disease patients in our study than in other studies. Moreover, this might be the reason for very low AUROC values compared with other studies discussed above. Not every patient with UGI bleeding underwent endoscopy, as the individual medical gastroenterologist made the decision on the need for an endoscopy and the type of intervention required for each patient. The severity of the disease was not the only factor that influenced the length of stay; patient's financial condition, and the physician's judgment could have played a role in deciding the length of hospital stay. The study was conducted in a single center with protocols for the management of the ED, but the decisions taken by the medical gastroenterologist such as time for endoscopy, blood transfusion, and length of stay may not have been uniformly protocol-driven. This may have influenced the results of predicting the need for endoscopic intervention and the duration of residence at the hospital equally in both the AIMS-65 and GBS.

## Conclusion

In our study, in-hospital mortality was the primary outcome; ICU disposition, the need for blood transfusion, endoscopic intervention, and the length of stay were secondary outcome measures. On comparing the AIMS-65 score with the GBS in patients with UGI bleeding, the AIMS-65 score was better in prognosticating the disposition of patients either to the ward or an ICU and in predicting in-hospital mortality. The GBS was only superior in prognosticating the need for transfusion of blood in patients with UGI bleeding. However, both scores could not predict the need for endoscopic intervention and the duration of stay at the hospital.

The AIMS-65 score had higher accuracy for predicting ICU or ward disposition and in-patient mortality. In conclusion, the AIMS-65 score is a simple, appropriate, non-endoscopic risk score that can be employed in patients with acute UGI bleeding, aiding in triage, early decision-making, and proper disposition from the ED. Therefore, the AIMS-65 score can be effectively applied in the ED. However, further studies may be required in multiple centers with a larger study population to validate the AIMS-65 score for the overall management of patients with UGI bleeding.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Sri Ramachandra University- Chennai (Ref: CSP-MED/14/FEB/12/29).

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

**Peer-review:** Externally peer-reviewed.

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

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

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EURASIAN JOURNAL OF EMERGENCY MEDICINE


# Evaluation of Characteristics and Clinical Outcomes of Patients with Cardiac Arrest

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## Abstract

**Aim:** Cardiopulmonary resuscitation (CPR) is an important and common intervention in emergency settings. In this article, we aimed to determine the characteristics and outcomes of the patients on whom CPR was performed in the emergency department (ED).

**Materials and Methods:** We retrospectively investigated the medical records of 295 patients with cardiopulmonary arrest over a two-year period. The patient's, age, sex, arrival time, route of arrival, reasons for admission, medical history, whether CPR was performed before arrival, whether intubation was performed, whether CPR was performed after arrival, whether defibrillation was performed, whether rapid sequence intubation (RSI) was performed, outcome (death, admission to an intensive care unit, an angiography unit, or a ward), and period of hospitalization were recorded.

**Results:** Most of the patients were brought by ambulance, and asystoly was the most common initial rhythm. In 182 patients, CPR was initiated before admission to the ED. All 26 patients with malignity died. Of the patients with a medical history of multiple diseases, 91.4% (n=32) died. RSI was performed in 19 patients (6.4%), and defibrillation was performed in 49 patients (16.6%). It was determined that 253 patients (85.8%) died after CPR.

**Conclusion:** In our study, asystoly was found to be the most common initial rhythm in patients with cardiopulmonary arrest. Our study also revealed that patients with co-morbidity and patients requiring RSI had lower rates of survival.

**Keywords:** Emergency department, cardiac arrest, cardiopulmonary resuscitation

## Introduction

Cardiopulmonary arrest (CPA) is defined as the sudden and unexpected interruption of respiration and/or circulation (1). In clinical practice, it refers to the "absence of cardiac mechanical activity." Clinical diagnosis is confirmed with unresponsiveness, pulselessness, and apnea. The term "cardiopulmonary resuscitation" (CPR) refers to interventions aimed to maintain vitality in a patient whose life is interrupted (2). In the US, 250,000–400,000 cardiac death incidents are reported annually. Cardiac deaths constitute 20% of all mortality in the western world (3, 4).

Resuscitation of a patient with CPA is a time-sensitive process that requires coordination between a number of health providers (5). It is accepted that outcomes of CPR depend on three basic factors–early and effective CPR, optimized response time, and early defibrillation. It is reported that early defibrillation within 5–7 minutes after sudden cardiac arrest increases survival up to 30–45% (6). As the time before CPR grows longer, the chance of survival decreases. Every extra minute decreases the survival rate by about 10% (7, 8).

In this study, our aim was to investigate the efficiency of updated CPR methods and Emergency Cardiac Care guidelines on the outcomes of CPR.

## Materials and Methods

In this cross-sectional retrospective study, medical records of patients of all ages who required CPR (n=295) in our emergency department (ED) were investigated between January 1, 2010, and December 31, 2011. Those who died before arrival to our ED (n=11) were excluded from the study.

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From the medical records, the patient's age, sex, arrival time, route of arrival, reasons for admission, medical history, whether CPR was performed before arrival, whether intubation was performed, whether CPR was performed after arrival, whether defibrillation was performed, whether rapid sequence intubation (RSI) was performed, outcome (death, admission to an intensive care unit, an angiography unit, or a ward), and the period of hospitalization were recorded.

**Statistical analysis**

For the statistical analysis, the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 15.0 program was used. Descriptive statistics were given as median and standard deviation for numeric variables and as number and percentage for categorical variables. The chi-square and Fisher's Exact tests were used for comparing categorical variables. Because numerical variables were not normally distributed between groups (Kolmogorov–Smirnov, $p<0.05$), the Mann–Whitney U test was used when comparing two groups and the Kruskal–Wallis H-analysis was used for comparing more than two groups. A p value<0.05 was considered statistically significant.

## Results

Of the 295 patients involved, 110 (37.3%) were female and 185 (62.7%) were male. The mean age of the patients was 64.13±18.9 years, and the mean age of males was significantly lower than females ($p<0.05$). [95% CI; (−14.5)–(−5.8)].

Patients were mostly admitted between 12:00 and 00:00 (n=187), and between the hours of 20:00 and 21:59 was the most common time of admittance.

Of the 230 patients admitted to the resuscitation room at the time of arrival, 78% had been brought by an ambulance.

When medical histories of the patients were investigated, it was determined that 26 patients (8.8%) had a malignity such as a unique disease and 35 patients (11.9%) had a history of multiple diseases. We could not determine the medical histories of 172 patients (58.3%).

Asystoly was the most common rhythm at the time of arrival (n=69, 23.4%) followed by ventricular fibrillation (VF) (n=31, 10.55%) and pulseless electrical activity (PEA) (n=25, 8.5%).

Cardiopulmonary resuscitation was performed in 223 patients (75.6%), and 195 (66.1%) were intubated only. In 182 patients, CPR was initiated before admission to the ED.

Rapid sequence intubation was performed in 19 patients (6.4%), and defibrillation was performed in 49 patients (16.6%).

It was determined that 253 patients (85.8%) died after CPR (85.9% of the 159 male patients died and 85.5% of the 94 female patients died). The difference between the sexes was not statistically significant ($p>0.05$).

All 26 patients with malignity died. Of the patients with a medical history of multiple diseases, 91.4% (n=32) died. Comparisons of these two variables with other parameters were statistically significant (Table 1).

Of the 139 patients who arrived in an ambulance, 60.4% died, and the mean length of hospital stay for patients arriving by ambulance was 4.2±14.5 days.

The rhythms of 86 patients could not be determined. The second-largest group was the asystoly group (n=63). Our study also revealed that 83 of the patients with unshockable rhythm on admission died (88.3%). A statistical significance was seen when patients were compared according to the initial rhythms (Table 2). Patients with asystoly on admission had the longest length of stay in the hospital when compared to other rhythms.

Patients who required RSI had a 0.24-fold greater risk of death when compared to those who did not. This finding was statistically significant (OR: 0.249, 95% CI: 0.092–0.675).

When laboratory findings of the patients were evaluated, it was determined that higher glucose levels were associated with higher mortality. Other parameters did not affect the mortality rate.

## Discussion

It is estimated that 60 million people die in the world annually, and ischemic heart diseases are the most common cause of death among adults (9-11). In the literature, the mean age of patients who die due to cardiac arrest is reported to be 68 years (12). The mean age of patients in our study was 64.1±19 years (60.3±19.2 years in males, 70.5±16.8 years in females). The lower age in our population is thought to be linked to socioeconomic and geographic factors.

**Table 1.** Comparison of outcomes of patients according to co-morbidities

| | Outcome | | | | Total | | | |
|---|---|---|---|---|---|---|---|---|
| | Death | | Discharge | | | | | |
| History | n | % | n | % | n | % | p | 95% CI |
| Malignity | 26 | 100.0 | - | 0.0 | 26 | 100.0 | | |
| Cardiac | 16 | 69.6 | 7 | 30.4 | 23 | 100.0 | | |
| Respiratory | 6 | 75.0 | 2 | 25.0 | 8 | 100.0 | | |
| Neurologic | 6 | 85.7 | 1 | 14.3 | 7 | 100.0 | | 0.000 |
| Kidney | 5 | 71.4 | 2 | 28.6 | 7 | 100.0 | 0.001 | – |
| Others | 10 | 58.8 | 7 | 41.2 | 17 | 100.0 | | 0.001 |
| Multiple | 32 | 91.4 | 3 | 8.6 | 35 | 100.0 | | |
| Unknown | 153 | 88.9 | 19 | 11.1 | 172 | 100.0 | | |
| Total | 254 | 86.1 | 41 | 13.9 | 295 | 100.0 | | |

**Table 2.** Outcomes of the patients according to initial rhythms

| Outcome | | Initial rhythm Total: Unshockable rhythm (Asystoly+PEA) n | % | Shockable rhythm (VF+Pulseless VT) n | % | Others (SR+AF+ Block+Unknown) n | % | Total n | % | p | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Death | n | 83 | 46.9 | 23 | 13.0 | 71 | 40.1 | 177 | 100.0 | | |
| | % | 88.3 | | 56.1 | | 44.4 | | 60.0 | | | |
| ICU | n | 6 | 8.1 | 13 | 17.6 | 55 | 74.3 | 74 | 100.0 | | |
| | % | 6.4 | | 31.7 | | 34.4 | | 25.1 | | | |
| Ward | n | 4 | 12.9 | 2 | 6.5 | 25 | 80.6 | 31 | 100.0 | | 0.001 |
| | % | 4.3 | | 4.9 | | 15.6 | | 10.5 | | 0.001 | - |
| Angiography | n | 1 | 16.7 | 3 | 50.0 | 2 | 33.3 | 6 | 100.0 | | 0.003 |
| | % | 1.1 | | 7.3 | | 1.3 | | 4.4 | | | |
| Surgery | n | 0 | 0.0 | 0 | 0.0 | 7 | 100.0 | 7 | 100.0 | | |
| | % | 00 | | 0.0 | | 4.4 | | 2.4 | | | |
| Total | n | 94 | 31.9 | 41 | 13.9 | 160 | 54.2 | 295 | 100.0 | | |
| | % | 100.0 | | 100.0 | | 100.0 | | 100.0 | | | |

PEA: pulseless electrical activity; VF: ventricular fibrillation; VT: ventricular tachycardia; SR: sinus rhythm; AF: atrial fibrillation; ICU: intensive care unit

In a study in Turkey, Erenler et al. (13) investigated trauma patients requiring CPR over a 5-year period and found the survival rate to be 9.5%. In our study, 14.2% of the patients were successfully resuscitated and survived. The reason for the greater survival rate in our study might be associated with the possibility of unpredictable injuries that multiple-trauma patients might have.

In a study by Wuerz et al. (14), it was reported that age did not affect the success of resuscitation. The main factors for success were reported to be early CPR and advanced cardiac life support, and our results are in agreement with the literature. Seven patients discharged after a successful resuscitation were over 80 years old.

In a study by Schears et al. (15), it was found that the success of CPR in patients with comorbid diseases, terminal cancer, and irreversible disease was low. In our study, the success of CPR in 123 patients with multiple diseases was lower than those with cancer alone.

Land ambulance was the most common route of arrival to the ED (78.5%), and the least common route was air ambulance (4%). Although there are reports in the literature that higher survival rates are obtained in patients arriving by air ambulance, we found no statistical significance between these two routes (16, 17). Patient transfer by air ambulance has only been present in Turkey since 2008, so it is still a developing field in the healthcare system.

Asystoly (44.2%), followed by VF (19.9%), were found to be the most common initial rhythms before cardiac arrest in our study. In the literature, it is reported that asystoly is more common than shockable rhythms (18). The higher frequency of unshockable rhythms might be associated with prolonged arrest, difficulties in recognizing cardiac arrest in a timely manner, or delayed activation of the emergency services. In developed countries, the frequency of VF outside of the hospital tends to decrease due to widespread use of automated external defibrillators in public places (19). Patients with PEA had the highest mortality rate (95.7%), followed by asystoly (88.4%). The majority of the patients who died (46.9%) had unshockable rhythms on admission. When all patients who required CPR were investigated, 34.7% had asystoly, and 88.4% of these patients died. In the literature, it is reported that CPR after asystoly has the lowest rate of survival (20).

In another study, it was determined that the most common initial rhythm in patients requiring CPR was asystoly (39%). In addition, when initial rhythms were investigated, the number of patients discharged from the hospital was found to be greater in patients with PEA when compared to those with asystoly and greater in patients with VT/VF when compared to those with PEA/asystoly. The hospital discharge rate was found to be higher in patients with shockable rhythms. Among unshockable rhythms, the discharge rate was higher in the PEA group than the asystoly group (21). In our study, PEA was found to have the highest mortality rate.

The mortality rate of patients on whom RSI was performed was lower than those who did not receive RSI (63.2% vs. 87.3%). Thus patients who underwent early airway protection had higher survival rates. This finding was also compatible with the literature where it is reported that RSI performed in the ED is both effective and safe (22).

We could obtain laboratory findings for 163 patients (55.2%) admitted to the resuscitation room. The glucose levels of 73.6% of the patients who died were high. It was also found that the AST and ALT levels of all the patients who required care in the resuscitation room were high. In the literature, there is a lack of laboratory investigations of patients who require CPR; however, in a previous study, an electrolyte imbalance was seen in 45% of the patients, and elevation of AST/ALT in patients admitted to the resuscitation room was also seen (23).

**Study limitations**

Our study also has some limitations. First, as mentioned above, we could not obtain medical records for 172 patients. Such a number

of patients without a medical record might affect our results regarding the relationship between cardiac arrest occurrence and co-morbidities. Second, we were unable to determine the initial rhythms of 86 patients due to the chaotic environment in the ED at the time of the patient's arrival. Third, it is possible that higher rates of RSI might have been obtained with an emergency team that was more experienced and skilled in the technique.

## Conclusion

Sudden cardiac death constitutes 20% of all deaths, and about half of these deaths occur in pre-hospital settings. Features associated with survival from CPA cases are known to be the presence of VF as the initial rhythm and early CPR either pre or in-hospital. Additionally, effective CPR in the ED, avoiding hyperventilation, and post-resuscitative care are other factors positively affecting mortality and morbidity. Our study revealed that patients with co-morbidity and patients requiring RSI had lower rates of survival.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of İzmir Katip Çelebi University (Decision No: 91, 10/12/2012).

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# An Emergency Medicine Perspective for Non-Convulsive Status Epilepticus Patients: Intravenous Midazolam

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## Abstract

Non-convulsive status epilepticus (NCSE) characterized primarily by changes in consciousness in association with typical electroencephalography (EEG) changes is not very common; however, it is usually difficult to diagnose this SE type. NCSE should be one of the differential diagnoses for patients who present to the emergency department with impaired consciousness. There is no standard approach in the literature proposed by emergency physicians for NCSE patients. It is understood from current literature that intravenous (IV) diazepam is the most commonly used first-line therapy following the diagnosis with EEG. In the two case reports, we analyzed our approach for the patients with known refractory epilepsy who presented to the emergency department due to somnolence based on the preliminary diagnosis of NCSE. In this context, we concluded that IV midazolam was a fast and effective agent to terminate seizure of patients with known refractory epilepsy.

**Keywords:** Emergency medicine, midazolam, non-convulsive status epilepticus

## Introduction

Status epilepticus (SE), which is a critical condition that must be intervened urgently, is characterized by seizures lasting for 5 minutes or longer on a continuous basis or two or more seizures without any improvement in consciousness (1). SE is divided to two groups as convulsive (CSE) and non-convulsive (NCSE) (2). NCSE accounts for 20%-25% of all SE cases (3). Although there are limited number of studies conducted on NCSE at emergency departments, there is no standard emergency approach developed for patients presenting with NCSE. Most of the studies of NCSE were performed by neurologists and anesthetists. In these studies, patients with NCSE were diagnosed with electroencephalography (EEG) and treated with IV diazepam or standard antiepileptics. However, the time to perform and interpret EEG at the emergency department is long for patients suspected to have NCSE; therefore, it will lead to a significant time loss for the termination of seizure. In this study, we emphasized the importance of IV midazolam to terminate seizures in 2 pediatric patients who presented to the emergency department due to impaired consciousness and were suspected to have NCSE.

## Case Presentations

### Case 1

A 15-year old male patient presented to the emergency department with impaired consciousness for about 40 minutes. When he was admitted to the emergency department, his eyes were open, but he did not respond to verbal stimuli. His vital signs were stable and he did not have high fever. He had a history of temporal lobe epilepsy diagnosed 5 years ago and thus underwent left temporal lobectomy 3 months ago. The patient was on quadruple antiepileptic treatment and adhered to the treatment completely. He neither had any comorbid diseases nor used any additional drugs recently. While he frequently experienced complex partial and secondary generalized seizures, he was suspected to have NCSE when he was admitted; therefore, electroencephalography (EEG) was performed. The spike-slow wave activity of a moderately high amplitude at 1–2 hz that was continuous on the right front–temporal region on EEG was considered as NCSE (Figure 1). In this context, midazolam from 0.05 mg up to 3 mg per kg was pushed intravenously (IV) to the patient who weighed approximately 60 kg. The patient regained his conscious-

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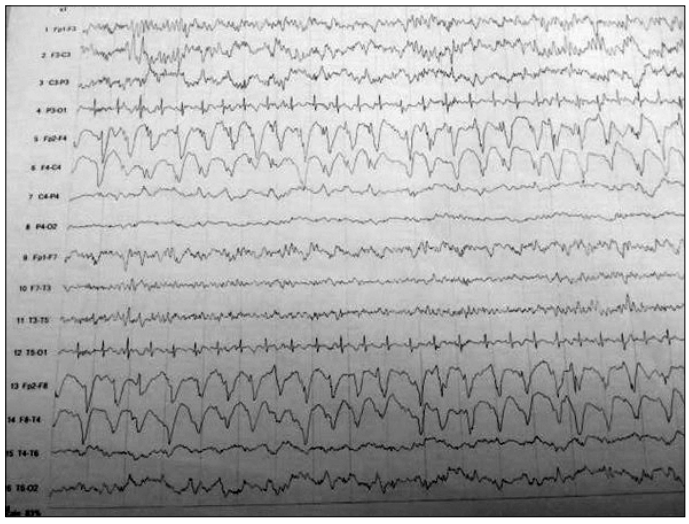

**Figure 1.** Electroencephalography of the first case before midazolam. Continuous spike-slow wave activity of moderately high amplitude at 1–2 hz in the right fronto–temporal region

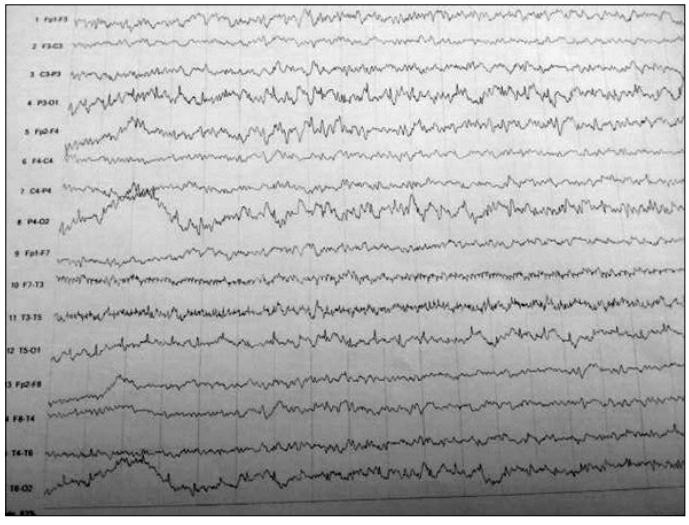

**Figure 2.** Electroencephalography showing the epileptic activity of the first patient suppressed after midazolam

ness within few minutes following midazolam; EEG was repeated and it was observed that the epileptic activity was suppressed (Figure 2). The cranial magnetic resonance imaging (MRI), and the cranial computerized tomography (CT) scan did not show any acute pathology. The laboratory parameters were within normal range, except for mild leukocytosis. The patient was observed for 6 hours at the emergency room and had full orientation and cooperation. Since he did not develop new seizures within that time, he was advised to visit the neurology polyclinic for control and was discharged from the emergency department.

**Case 2**

A 16-year old patient with epileptic seizures secondary to known schizencephaly was presented to the emergency department with impaired consciousness. He had been staring into space for a few seconds in the past month, while he had impaired consciousness since he did not respond to the verbal and painful stimuli for 2 hours on the day of admission. Despite the antiepileptic drugs, he intermittently experienced complex partial and secondary generalized seizures. He did not have any additional disease and a history of additional drug use. He did not have fever and his vital signs were stable when he was admitted to the emergency department. The patient who had grade 2 obesity was suspected to have NCSE that led to impaired consciousness and thus after he was monitored, he was given 4 mg (0.05 mg/kg) IV midazolam. He regained his consciousness in a few minutes after the administration of midazolam, with full recovery in 1 hour. His cranial MRI and CT scans did not show any acute pathology. His laboratory parameters were stable. Antiepileptic treatment was prescribed in consultation with the neurology department, and he was discharged from the emergency department after a 6-hour follow-up since did not experience a new seizure.

## Discussion

Non-convulsive is a neurological emergency that is characterized by a variety of clinical conditions from confusion to coma. While it is difficult to recognize NCSE patients, the gold standard for diagnosis is EEG (4). EEG of NCSE patients shows continuous or intermittent electrographical discharges (5). Studies have shown that EEG might be useful to diagnose the NCSE patients who are admitted to the emergency department due to changes in the mental status (6, 7). We diagnosed our first patient through EEG. However, we did not deem it necessary to perform EEG for the second patient due to his history of schizencephaly, typical clinical manifestations, and based on our previous experience. It may take almost 1 hour to perform and interpret EEG of a patient who is admitted to the emergency department for suspected seizure. This will mean that the patient will have seizures for an additional 1 hour. Considering some of the technical challenges, this time may further increase. In fact, we terminated the seizure of the second patient more rapidly compared to the first patient.

The main clinical manifestations of NCSE patients include tendency to sleep and changes in consciousness (8). Similarly, both cases presented to the emergency department due to changes in consciousness. Studies show that most of the NCSE patients have known epilepsy similar to our cases (9).

The studies conducted on the termination of seizures in NCSE patients at the emergency department are limited, whereas the medications used for standard SE patients are known to have benefits (10). In a review by Maganti et al. (8) on NCSE, they reported that IV benzodiazepines could be given as first-line therapy followed by IV phenytoin, phenobarbital, or valproic acid. Levatiracetam has become a commonly used agent for SE at emergency departments, particularly for pediatric patients (11). In a retrospective study conducted by Osorio et al. (12), they found that the epileptiform waves of refractory SE patients who were administered IV 10 mg diazepam were suppressed on EEG. Similarly, in a single-case study by Akpınar et al. (13), they used 10 mg IV diazepam as first-line therapy to terminate NCSE caused by an infection. Moreover, in a case series including 7 patients who developed NCSE due to cephalosporins, all patients were successfully treated with IV diazepam (14). Contrary to these studies, we used midazolam that was more rapid and short acting to terminate seizures of our patients compared to diazepam. Both patients responded rapidly to midazolam. Furthermore, patients experienced no side effects.

## Conclusion

When patients with known refractory epilepsy present to the emergency department with impaired consciousness with typical manifestations of NCSE, such as dull gaze and lack of response to verbal stimuli, they can be treated with midazolam, which is one of the fast-acting benzodiazepines without the need for EEG.

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**Peer-review:** Externally peer-reviewed.

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# Acute Respiratory Distress Syndrome and Pneumothorax after Synthetic Cannabinoid Intoxication

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## Abstract

Synthetic cannabinoids, whose effects are derived from CB1 and CB2 receptors in the nervous system, have come to represent a significant public health problem with the rapid increase in their use in the young and adult population. Synthetic cannabinoids are known as Spice in Europe, K2 in America, and bonsai or Jamaica in Turkey. A 25-year-old male was brought to the emergency department after being found by relatives in an unconscious state. Respiratory arrest developed, and the patient was intubated. Preliminary diagnoses of bonsai intoxication and respiratory failure were made, and the patient was transferred to our university hospital intensive care unit. Acute respiratory stress syndrome developed during monitoring. Mechanical ventilatory support was administered in the intensive care unit. Respiratory difficulty and chest pain developed one day after extubation. Chest radiography revealed pneumothorax in the left lung, and a chest tube was inserted. The patient was discharged in a healthy condition on the 11$^{th}$ day of hospitalization. Respiratory depression and acute pulmonary injury can develop in patients with bonsai intoxication.

**Keywords:** Bonsai, respiratory depression pneumothorax, synthetic cannabinoid

## Introduction

Bonsai, which contains various different synthetic cannabinoids (SCs) is widely used by young people because it is cheaper and more easily available than narcotic drug,marijuana and cocaine (1). The most common side effects are sweating, tachycardia, tremor, nausea, vomiting, hyper/hypotension, agitation, confusion, and respiratory depression.

This report describes the case of a patient with respiratory depression and acute respiratory distress syndrome (ARDS) developing following bonsai use and subsequent pneumothorax. It also discusses the side effects of bonsai use in the respiratory system and provides information from the literature.

## Case Presentation

A 25-year-old male was found unconscious at home by relatives and was brought to a nearby emergency department. At his initial examination, his general condition was poor and he was unconscious. Respiratory arrest developed, and he was intubated. SC intoxication and respiratory failure were diagnosed in light of the history of bonsai use. On the second day, he was referred to our university hospital intensive care unit from the state hospital. Mechanical ventilatory support was administered. Widespread bilateral infiltration was observed on the posteroanterior chest radiography on the second day of hospitalization. On the second day, his blood gas pH was 7.18, arterial partial pressure of oxygen ($PaO_2$) was 140 mmHg, arterial partial pressure of carbon dioxide ($PaCO_2$) was 65 mmHg, bicarbonate ($HCO_3$) was 18 mmol/Land oxygenation index ($PaO_2/FiO_2$)was 140 mmHg; in the light of the sudden onset, bonsai intoxication-related ARDS was suspected. The mechanical ventilator employed due to ARDS was adjusted to a tidal volume of 5–7 mg/kg, high positive end-expiratory pressure (PEEP) and daily blood gas values. On the eight day of hospitalization, his GCS score was 14, blood gas pH was 7.39, $PaO_2$ was 260 mmHg, $PaCO_2$ was 43 mmHg, $HCO_3$ was 26 mmol/Land $PaO_2/FiO_2$ was 577 mmHg. A sufficient tidal volume was achieved at low pressures. The patient met the weaning criteria and was extubated. Sudden-onset respiratory difficulty and chest pain developed the following day. Posteroanterior chest radiography was performed. Pneumothorax was detected in the left lung, and tube thoracostomy was performed (Fig-

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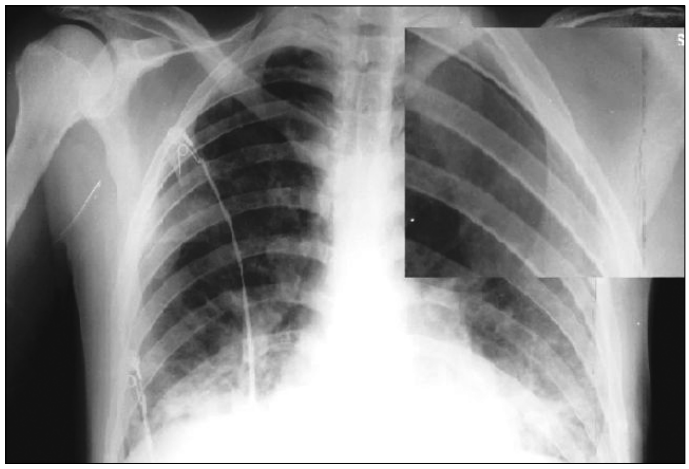

**Figure 1.** Visceral pleural margin (small image) of pneumothorax developing in the left lung on performing posteroanterior chest radiography

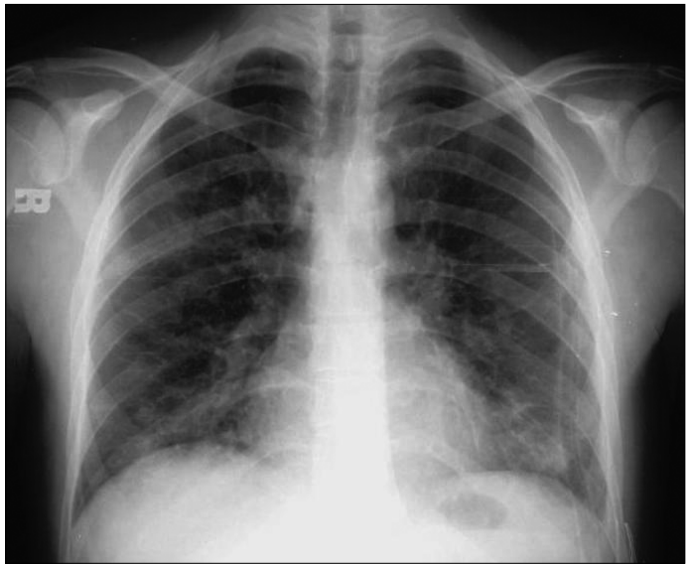

**Figure 2.** Control posteroanterior chest radiograph after the drain was removed

ure 1). The drain tube was removed in the absence of air leakage from the drain; pneumothorax was not seen on performing control radiography (Figure 2). His GCS score was 15, and his general condition was good and vital findings were stable. There was no respiratory difficulty, and he was discharged in a healthy condition on the 11th day of hospitalization.

## Discussion

SCs were initially used in Europe and then gradually spread worldwide (2). The American Association of Poison Control Centers reported 53 cases of exposure to bonsai in 2009 and 13,000 cases in 2011 (3). This increase is responsible for tremendous increase in bonsai use in Turkey, despite the absence of official figures to date. We attribute this increase to the low cost of bonsai and its easy availability that is associated with the absence of supervision among the young, urban population.

Similar to marijuana, the chronic use of SCs leads to dependence syndrome, withdrawal symptoms, and psychiatric symptoms (1). However, in contrast to marijuana, acute intoxication findings more closely resemble those seen during sympathomimetic drug use. Despite frequent side effects involving the cardiopulmonary system, such as hyper/hypotension, confusion, and respiratory depression, clinical symptoms and presentations can vary. In the management of SC toxicity, supportive treatment, such as fluid and electrolyte replacement, benzodiazepines for agitation and anxiety, and non-invasive or invasive ventilatory support for respiratory failure, has been suggested (4, 5).

In a study in Turkey, Köklü et al. (6) reported myocardial infarction following bonsai use. In our case, respiratory arrest following bonsai use and pneumothorax developed after ARDS. We attribute this to SCs causing toxic injury to the pulmonary parenchymal tissue. SCs causing vasoconstriction and endothelial dysfunction and resulting in injury by creating nutrition problems in the peripheral pulmonary parenchyma may account for the pathophysiology of the respiratory side effects in our patient. Kaya et al. (5) reported a decrease in clinical findings at the 3-h observation after bonsai use. However, this may vary depending on the variety of SCs in the bonsai used and the intake amount. The pulmonary complications developing in our patient persisted until the 10th day after substance use. Therefore, we think that it is important for physicians who monitor such patients to keep the monitoring or hospitalization period relatively lengthy to be able to recognize such potential complications.

## Conclusion

Severe respiratory depression and ARDS can develop in association with bonsai use. The development of pneumothorax can be a complication of respiration with mechanical ventilation in ARDS patients. The close monitoring of respiratory functions during the monitoring of such patients and the careful evaluation of pulmonary X-rays will permit the early diagnosis and treatment of pulmonary complications.

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

**Peer-review:** Externally peer-reviewed.

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

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# A Huge Morgagni Hernia in a 62-Years-Old Female Patient

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A 65-years-old female patient was admitted to our emergeny department with severe intermittent epigastric pain, which radiated to the right thoracic region. She had an ongoing intermittent epigastric pain since a week. On physical examination, decreased breath sounds in the right hemithorax and epigastric tenderness were found. Laboratory examination detected no abnormal findings except mild leukocytosis. On plain chest roentgenogram, a large soft tissue mass containing a portion of opacified colonic structure filled with the remnant of a previously performed barium enema was observed in the right hemithorax (Figure 1). A thoracoabdominal CT revealed a herniated colonic segment and omentum in the right hemithorax. The patient underwent surgery, and an ischemic herniated transverse colonic segment and omentum, which passed to the right hemithorax through the right anterior sternocostal defect (Morgagni's hernia) were detected. After reduction of the herniated colonic segment and omentum, the diaphragmatic hernia was repaired using prolene mesh.

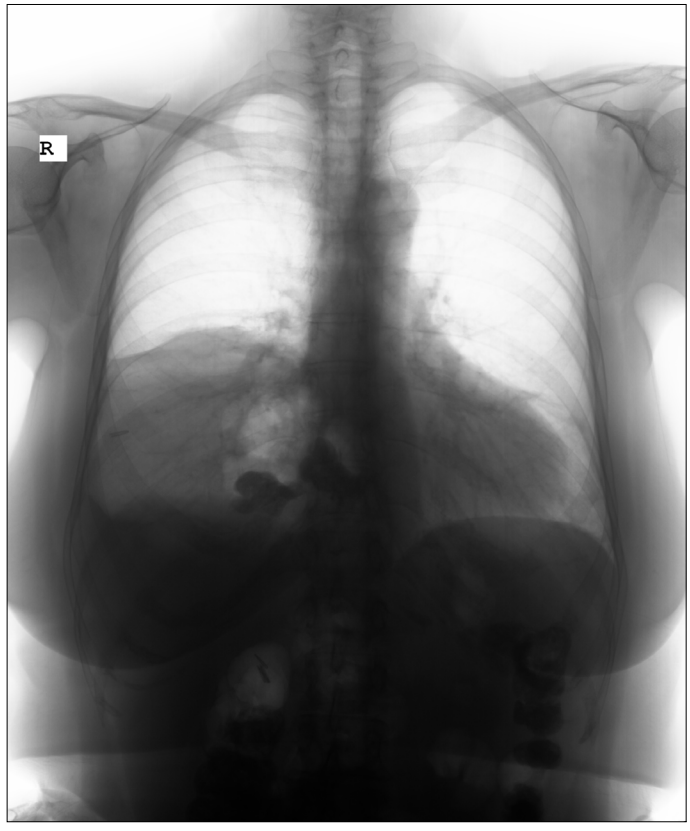


**Figure 1.** An image of the huge Morgagni's hernia on plain chest roentgenogram

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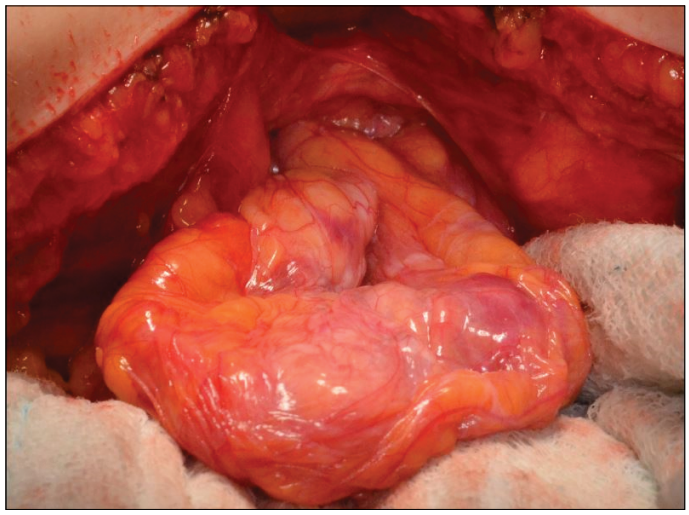

**Figure 2.** A view of the huge Morgagni's hernia reduced into the abdominal cavity

## Discussion

Morgagni's hernia can be defined as the protrusion of any abdominal content into the thoracic cavity through the congenital anterior sternocostal defect. Morgagni's hernia was first described by the Italian anatomist and pathologist Morgagni in 1769 (1). Morgagni's hernia is a rare condition and constitutes approximately 2%-3% of congenital diaphragmatic hernias. It is usually found on the right side of the diaphragm and rarely on the left (2). Hernial defect repair without removing hernial sac is the most common surgical procedure, which can be performed via abdominal, thoracic, or laparoscopic approaches. Although Morgagni's hernia is a congenital diaphragmatic hernia, it is rarely seen in adults. Pulmonary and epigastric complaints are the most common symptoms in adult Morgagni's hernia cases, which can be complicated by strangulation or obstruction (3). In our case, strangulation findings recovered with reduction were observed in the herniated transverse colon segment. Adult Morgagni's hernia is a very rare condition, and immediate surgical intervention may be required in some cases.

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