An update to this article is included at the end

American Journal of Emergency Medicine 38 (2020) 1910–1914

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Clinical use of copeptin in migraine patients admitted to the emergency department☆,☆☆

Derya Yalçın Yılmaz [a], Hamit Hakan Armağan [b], Kıvanç Karaman [b,*], Fevziye Burcu Şirin [c], Mustafa Bozkurt [c], Adnan Karaibrahimoğlu [d], İsa Gökhan Yalçın [e], Nesrin Gökben Beceren [b], Önder Tomruk [b]

[a] Emergency Department of Çankırı State Hospital, Çankırı, Turkey
[b] Medical Faculty of Suleyman Demirel University, Emergency Medicine Department, Isparta, Turkey
[c] Medical Faculty of Suleyman Demirel University, Department of Biochemistry, Turkey
[d] Medical Faculty of Suleyman Demirel University, Department of Bioistatistics and Medical Informatics, Turkey
[e] Emergency Department of Isparta State Hospital, Isparta, Turkey

ARTICLE INFO

Article history:
Received 5 February 2020
Received in revised form 4 March 2020
Accepted 3 May 2020

Keywords:
Copeptin
Emergency
Headache
Migraine

ABSTRACT

Purpose: The purpose of this study was to investigate the clinical use of copeptin to evaluate migraine attacks in the Emergency Department. An additional aim was to detect changes in serum copeptin levels in migraine patients during attack and attack-free periods.
Methods: This prospective case–control study included 52 migraine patients and 51 healthy individuals with similar demographic characteristics. Blood samples were collected from migraine patients both in attack and attack-free periods.
Results: The mean copeptin levels in the patients group in the attack and attack-free periods were 689.28 and 576.68 pg/ml, respectively, whereas they were 608.68 pg/ml in the control group. There was a significant difference in the mean copeptin level in the attack period and attack-free periods ($p = 0.026$). The sensitivity and specificity of copeptin in detecting headache episodes in migraine patients were 58.8% and 60.7%, respectively, at a cut-off value of 388.67 pg/ml.
Conclusion: This is the first study to investigate the diagnostic efficacy of serum copeptin levels in migraine patients. Although the diagnostic efficacy of serum copeptin levels for migraines was unsatisfactory, it could be helpful at management of migraine patients in ED.

© 2020 Elsevier Inc. All rights reserved.

1. Introduction

Headaches are a very common presenting symptom in the emergency department (ED). The differential diagnoses of headaches range from benign pathologies, such as a migraine and other primary headache syndrome, to life-threatening pathologies, such as a subarachnoid hemorrhage. Migraines, which are a common primary headache syndrome, are an important cause of patients presenting to the ED with headaches. As the diagnosis of a migraine is based on clinical symptoms rather than on laboratory and imaging methods, migraines pose a clinical challenge for emergency physicians. This clinical challenge sometimes leads to unnecessary examinations in patients. Furthermore, it may lead to misdiagnoses of more critical pathologies in some cases.

Classical vascular theory was the first scientific hypothesis put forward to explain the pathophysiology of a migraine. According to this theory, long-term vasodilatation following vasoconstriction of intracranial arteries during a migraine attack may cause headaches and other symptoms [1]. Based on this theory, the effectiveness of various biomarkers in the diagnosis of a migraine has been investigated. In their study in 1991, Hamptom et al. reported that arginine vasopressin (AVP), an important stress hormone with hemodynamic, endocrinological, and neurological effects may be useful in the diagnosis of a migraine [2]. However, various features of AVP, such as its instability, short half-life, and binding to platelets in plasma, preclude its use daily medical practice [3]. Recently, copeptin, a peptide that is co-released with AVP in equal amounts, has emerged as a marker of serum AVP and related pathologies [4-7]. The diagnostic and prognostic value of copeptin have been demonstrated in many pathologies associated with headaches, such as nontraumatic headaches, strokes, subarachnoid hemorrhages, and traumatic brain injuries [7,8].

☆ This work was performed in Medical Faculty of Suleyman Demirel University, Emergency Medicine Department.
☆☆ This study has not been published or presented before and is not currently being considered for publication elsewhere.
* Corresponding author.
E-mail address: kivanckaraman@sdu.edu.tr (K. Karaman).

https://doi.org/10.1016/j.ajem.2020.05.009
0735-6757/© 2020 Elsevier Inc. All rights reserved.

The purpose of this study was to investigate the clinical use of copeptin to evaluate migraine attacks in the Emergency Department. An additional aim was to detect changes in serum copeptin levels in migraine patients during attack and attack-free periods.

2. Methods

2.1. Study population

This was a prospective case–control study conducted in the ED of a tertiary university hospital. Patients aged between 18 y and 60 y who had a previous diagnosis of migraine and admitted to the ED with usual headache episode and were evaluated as migraine attack between July 2018 and April 2019 were included. After obtaining written consent, blood samples were taken from the participants. Each participant was asked to revisit the ED in the attack-free period (a minimum of 1 wk. and a maximum of 4 wk. after the migraine attack), at which time another blood sample was taken. A migraine was diagnosed according to the classification of the most recent diagnostic criteria of International Headache Disorders accepted by the World Health Organization and World Neurology Federation [9]. Patients were excluded if they had any other acute or chronic illnesses, a history of trauma within the last week, a history of alcohol or corticosteroid use within the last week, or any underlying morbidity that could cause headaches. Patients who were pregnant were also excluded.

The control group consisted of healthy volunteers with a similar age and sex distribution to those included in the patient group. After obtaining written consent, all the participants underwent a detailed neurological examination.

2.2. Ethics

The study was performed in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the local ethics committee (protocol code: 2018/163), and written informed consent was obtained from all the participants.

2.3. Sample collection and preparation

Peripheral venous blood samples from the patient group and control group were collected in gel-containing biochemistry tubes. The tubes were centrifuged at 3000 rpm for 10 min, and the collected serum samples were stored at −80 °C until the analysis.

2.4. Measurement of serum copeptin levels

Quantitative measurement of serum copeptin levels was performed using a commercial ELISA kit (Human Copeptin (CPP) ELISA Kit, *E*-EL-H0851, Elabscience, Wuhan, China) according to the manufacturer's instructions. A calibration curve was generated by measuring the standard concentrations, and the copeptin concentration in each sample was determined by interpolation from the calibration curve. The detection limit of the assay was 18.75 pg/ml.

2.5. Statistical analyses

The statistical analyses were performed using SPSS 20.0 (IBM Inc., Chicago, IL, USA). Descriptive statistics are presented as the mean ± SD for numerical variables and frequency (percentage) for categorical variables. The Kolmogorov–Smirnov method was used to test the normality of the copeptin data. Between-group comparisons were performed using the Mann–Whitney *U* test. As the distribution of the data was not normal, paired sample comparisons were performed using Wilcoxon's signed-rank test. A chi-square test was used for sex variables, and the relation between the age of the patients and the measurements was determined by Spearman's Rho correlation analysis. A power analysis was conducted using GPower 3.1.0 software (Universiaet Kiel). The same software was used for determination of the sample size. Based on the results, it was calculated that 50 patients were sufficient to reach 80% power. A value of $p < 0.05$ was considered statistically significant, with a type-I error of 5%.

3. Results

Of 917 patients admitted to the ED with a headache during the study period, 164 patients were diagnosed with a migraine. Of these, 87 patients agreed to participate in the study. Among these 87 patients, 34 patients refused to give a blood sample again in the attack-free period, and one patient was excluded due to a failure in the storage process of the frozen blood sample. Finally, 52 migraine patients and 51 healthy individuals with similar demographic characteristics were enrolled in the study. The flow chart of the study and demographic features of the participants are given in Fig. 1 and Table 1, respectively.

As shown in Fig. 2, the mean copeptin level was higher in migraine-attack periods and lower in attack-free periods in the patient group as compared with that in the control group. Although the distribution of copeptin values and standard deviations are wide, there was a statistically significant difference between the mean copeptin levels of migraine patients in attack and attack-free periods ($p = 0.026$) (Table 2).

The diagnostic performance of copeptin in detecting headache episodes of migraine was evaluated by a receiver operating curve analysis. Copeptin had sensitivity of 58.8% and specificity of 60.7% at a cut-off value of 388.67 pg/ml. More detailed information is provided in Fig. 3.

4. Discussion

We hypothesized that serum copeptin levels may have diagnostic value in migraine patients who were admitted to the ED with headaches. To our knowledge, this study is the first to evaluate the role of copeptin in migraine patients. The majority of migraine patients in this study were middle-aged women. The sex and age distribution of the migraine patients in our study were similar to those in other studies [10,11]. Therefore, our results can likely be extrapolated to the general population.

The headache that occurs during a migraine is thought to be related to activation of the trigeminovascular system and the release of various neurotransmitters, leading to an inflammatory cascade involving the meninges, meningeal arteries and veins, and cortical substances [12]. The diagnosis of a migraine is based on a detailed medical history, subjective clinical criteria, and exclusion of conditions mimicking migraine [9]. With advances in migraine research, various biomarkers, such as glutamate, calcitonin gene-related peptide, β-endorphin, and pentraxin-3, have been identified [13]. However, the optimal use of these biomarkers in diagnosis, prognosis, and treatment remain to be determined. Thus, in the present study, we aimed to determine the utility of copeptin as a diagnostic parameter in migraine attacks. Our study demonstrated that copeptin levels in migraine patients during both attack and attack-free periods were not significantly different from those of a control group. Hence, copeptin levels do not appear to have diagnostic value in migraines.

The most important finding of our study was the significant increase in copeptin levels in migraine patients during the attack period. In the ED management of headaches, a diagnosis of a migraine can be made if patients report they are having a typical migraine attack or an exacerbation of a recurrent headache disorder that clearly meets established migraine criteria. However, for patients with atypical presentations or with a headache that in some way differs from their usual pattern or does not respond to usual medications, it is often unclear whether further diagnostic workup is indicated [14]. The numbers of neuroimaging requests in the ED and cost of neuroimaging have increased in recent decades [15]. Our study demonstrated that at a cut-off value of 388.67 pg/ml, copeptin had 58.8% sensitivity and 60.7% specificity in detecting

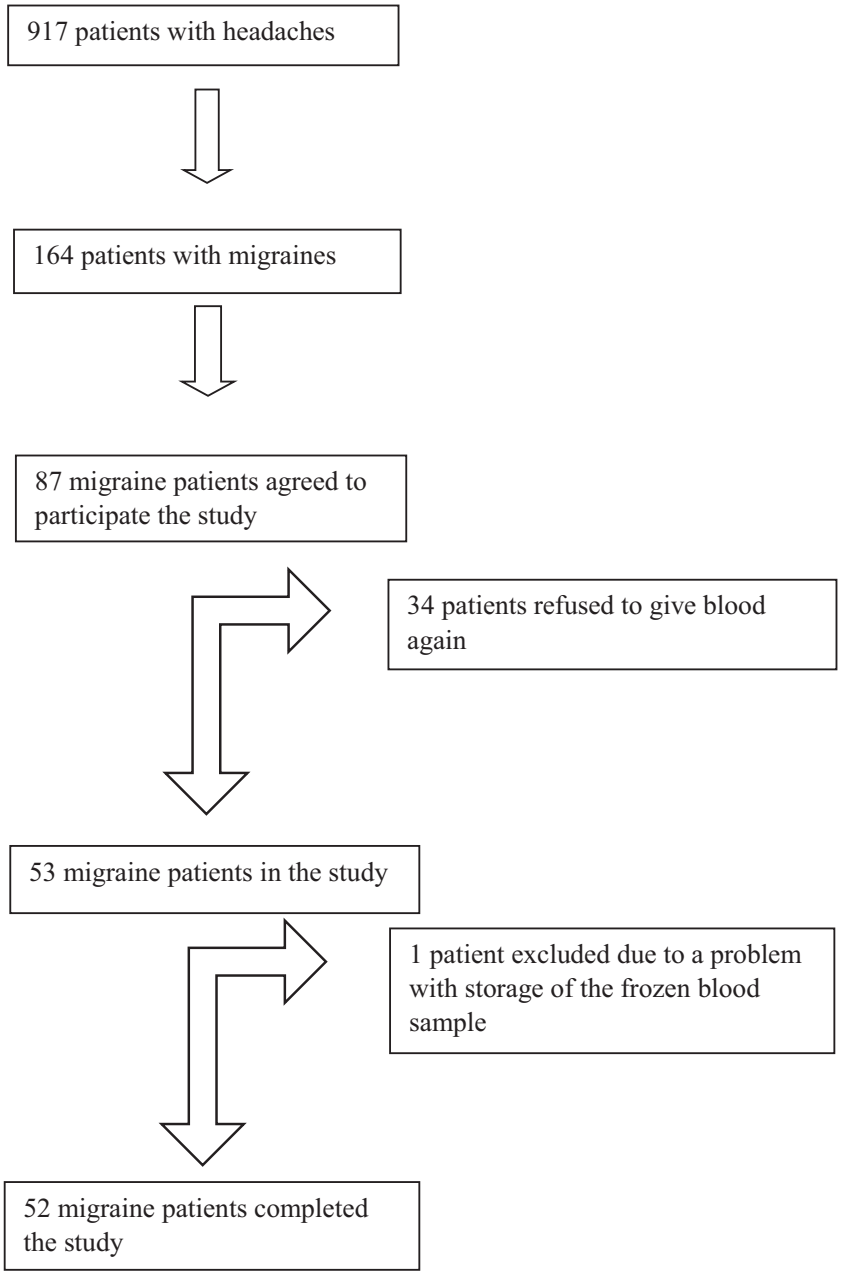


Fig. 1. Flow chart of the study.

a headache attack in migraine patients. In terms of the clinical value of this finding, it could be helpful for emergency physicians in the evaluating of migraine attacks in ED.

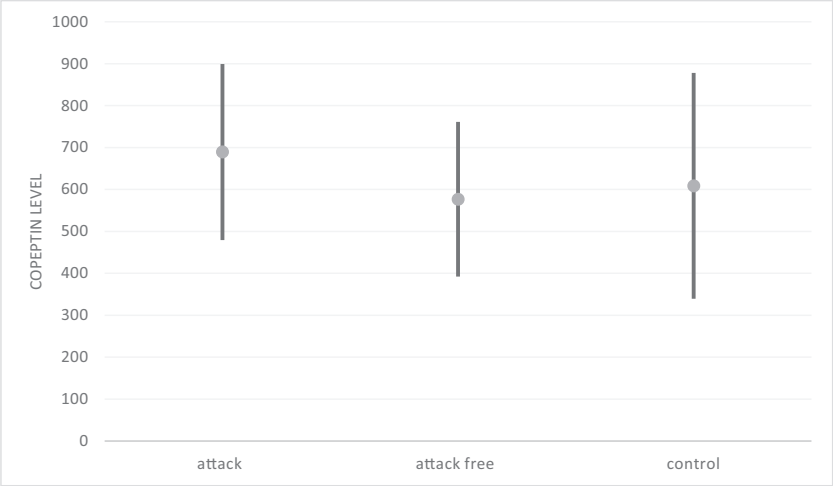
A number of previous studies have established the diagnostic efficacy of AVP levels in migraine patients. For example, in a study on 14 migraine patients in 1991, Hamptom et al. showed that the serum AVP level increased significantly during the attack period [2]. Hasselblatt et al. demonstrated that AVP levels increased in migraine patients within hours of an attack [16]. The results obtained in the present study support those of these earlier studies. However, considering various features of AVP, such as its instability, short half-life, and binding to platelets, we think that copeptin may be more suitable than AVP is for use in clinical practice.

This study has some limitations, such as its single-center design and lack of assessment of migraine symptoms and auras. The small sample size was an additional limitation. Another limitation was that the participants were not questioned about the time between the onset of symptoms and the attack at the time of blood sampling. In an earlier study, the AVP level increased in the first 3 h of an attack and remained high as long as symptoms persisted [x]. Thus, we think that this limitation would not have affected the results of the present study.

To conclude, this is the first study to investigate the diagnostic efficacy of serum copeptin levels in migraine patients. Although the diagnostic efficacy of serum copeptin levels for migraines was

Table 1
Demographic features of the participants

	Patients (n:52)	Controls (n:51)	p Value
Sex (male/female)	10/42	10/41	0.962
Age (y)	32.84 ± 9.94	33.12 ± 9.65	0.879

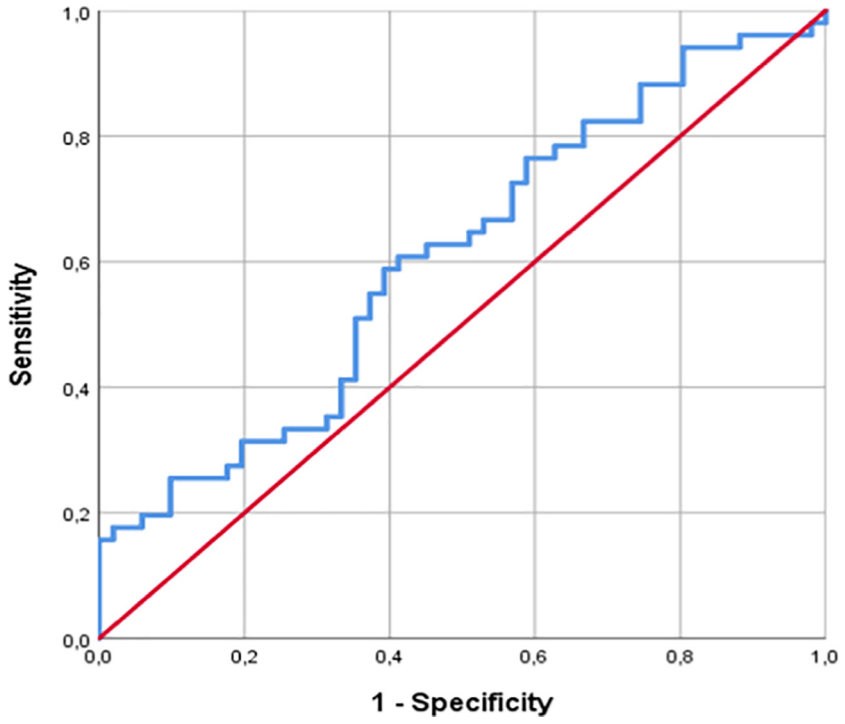


*The data ranges in the figure reflect 95% CI values.

Fig. 2. Mean copeptin levels of patients during migraine attack and attack-free periods and mean copeptin levels in the control group. *The data ranges in the figure reflect 95% CI values.

Table 2
Between-group comparison of copeptin levels

	Copeptin level (pg/ml)	p Value
Attack period versus control	689.28 ± 730.36 versus 608.68 ± 950.70	0.069
Attack free period versus control	576.68 ± 639.95 versus 608.68 ± 950.70	0.984
Attack period versus attack-free period	689.28 ± 730.36 versus 576.68 ± 639.95	**0.026**



AUC (95% CI)	0.607 (0.497-0.716)
Cut-off	388.67
Sensitivity (%)	58.82 (44.17-72.42)
Specificity (%)	60.78 (46.11-74.16)
PPV (%)	60.00 (49.84-69.36)
NPV (%)	59.62 (49.86-68.67)

AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value

Fig. 3. Receiver operating characteristic curve and performance of copeptin in detecting headache episodes in migraine patients. AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value.

unsatisfactory, measurements of serum copeptin levels may be effective in reducing unnecessary imaging costs, especially in migraine patients with an atypical clinical presentation. More comprehensive studies are needed to support our findings.

Author contributions

Derya YALÇIN YILMAZ: Conceptualization, Methodology, Investigation, Data Curation, Resources, Writing-Original draft preparation, Writing-Reviewing and Editing.

Hamit Hakan ARMAĞAN: Conceptualization, Methodology, Visualization, Supervision.

Kıvanç KARAMAN: Writing-Original draft preparation, Writing-Reviewing and Editing, Supervision.

Fevziye Burcu ŞİRİN: Data Curation, Resources, Investigation.

Mustafa BOZKURT: Data Curation, Resources, Investigation.

Adnan KARAİBRAHİMOĞLU: Methodology, Data Curation, Formal analysis.

İsa Gökhan YALÇIN: Investigation, Resources, Data Curation.

Nesrin Gökben BECEREN: Visualization, Supervision, Data Curation.

Önder TOMRUK: Visualization, Supervision, Investigation.

Acknowledgements

None.

References

[1] Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211https://www.ichd-3.org/2019.

[2] Dodick DW. Migraine. Lancet. 2018;391(10127):1315–30.

[3] Gokdemir MT, Nas C, Gokdemir GS. Pentraxin 3 level in acute migraine attack with aura: patient management in the emergency department. Am J Emerg Med. 2019. https://doi.org/10.1016/j.ajem.2019.04.004 In press.

[4] Friedman BW. Migraine in the emergency department. Neurol Clin. 2019;37:743–52.

[5] Gilbert JW, Johnson KM, Larkin GL, Moore CL. Atraumatic headache in US emergency departments: recent trends in CT/MRI utilisation and factors associated with severe intracranial pathology. Emerg Med J. 2012;29(7):576–81.

[6] Hampton KK, Esack A, Peatfield RC, Grant PJ. Elevation of plasma vasopressin in spontaneous migraine. Cephalalgia. 1991;1(6):249–50.

[7] Hasselblatt M, Köhler J, Volles E, Ehrenreich H. Simultaneous monitoring of endothelin-1 and vasopressin plasma levels in migraine. NeuroReport. 1999;10(2):423–5.

[8] Silberstein SD. Migraine pathophysiology and its clinical implications. Cephalalgia. 2004;24:2):2–7.

[9] Morgenthaler NG, Struck J, Jochberger S, Dünser MW. Copeptin: clinical use of a new biomarker. Trends Endocrinol Metab. 2008;19(2):43–9.

[10] Dobsa L, Edozien KC. Copeptin and its potential role in diagnosis and prognosis of various diseases. Biochem Med (Zagreb). 2013;23(2):172–90.

[11] Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. Peptides. 2005;26(12):2500–4.

[12] Balanescu S, Kopp P, Gaskill MB, Morgenthaler NG, Schindler C, Rutishauser J. Correlation of plasma copeptin and vasopressin concentrations in hypo-, iso-, and hyperosmolar states. J Clin Endocrinol Metab. 2011;96(4):1046–52.

[13] Katan M, Müller B, Christ-Crain M. Copeptin: a new and promising diagnostic and prognostic marker. Crit Care. 2008;12(2):117.

[14] Nickel CH, Bingisser R, Morgenthaler NG. The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. BMC Med. 2012;10:7.

[15] Stovner LJ, Zwart JA, Hagen K, Terwindt GM, Pascual J. Epidemiology of headache in Europe. Eur J Neurol. 2006;13(4):333–45.

[16] Stovner LJ, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia. 2007;27(3):193–210.

Update

American Journal of Emergency Medicine
Volume 38, Issue 12, December 2020, Page 2762

DOI: https://doi.org/10.1016/j.ajem.2020.08.002

American Journal of Emergency Medicine 38 (2020) 2762

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Corrigendum

Corrigendum to "Clinical Use of Copeptin in Migraine Patients Admitted to the Emergency Department" [American Journal of Emergency Medicine, Volume 38, Issue 9, September 2020, P1910–1914]

Derya Yalçin Yilmaz [a], Hamit Hakan Armağan [b], Kıvanç Karaman [b,*], Fevziye Burcu Şirin [c], Mustafa Bozkurt [c], Adnan Karaibrahimoğlu [d], İsa Gökhan Yalçin [e], Nesrin Gökben Beceren [b], Önder Tomruk [b]

[a] Emergency Department of Çankırı State Hospital, Çankırı, Turkey
[b] Medical Faculty of Suleyman Demirel University, Emergency Medicine Department, Isparta, Turkey
[c] Medical Faculty of Suleyman Demirel University, Department of Biochemistry, Isparta, Turkey
[d] Medical Faculty of Suleyman Demirel University, Department of Bioistatistics and Medical Informatics, Turkey
[e] Emergency Department of Isparta State Hospital, Turkey

The authors regret <The funding information is absent. This study was supported by Suleyman Demirel University Scientific Research Projects Coordination Unit (project no:TTU-2018-6803)>.

The authors would like to apologise for any inconvenience caused.

DOI of original article: https://doi.org/10.1016/j.ajem.2020.05.009.
* Corresponding author at: Medical Faculty of Suleyman Demirel University, Emergency Medicine Department, 32260 Isparta, Turkey.
E-mail address: kiwanckaraman@gmail.com (K. Karaman).

https://doi.org/10.1016/j.ajem.2020.08.002
0735-6757/© 2020 Elsevier Inc. All rights reserved.